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(54) **PRODUCTION OF A CYSTEINE RICH PROTEIN**

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A61K 39/015	(2006.01)
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C12P 21/02	(2006.01)
C12N 15/62	(2006.01)
C12N 15/74	(2006.01)

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CPC ***C07K 14/445*** (2013.01); ***A61K 39/015*** (2013.01); ***C07K 14/4718*** (2013.01); ***C12N 15/62*** (2013.01); ***C12N 15/746*** (2013.01); ***C12P 21/02*** (2013.01); *C07K 2319/055* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to a method for the production of correctly folded Pfs48/45. This is achieved in the *lactococcus lactis* when Pfs48/45 or fractions thereof are fused genetically to a glutamate rich protein, e.g. GLURP from *Plasmodium falciparum.*

20 Claims, 9 Drawing Sheets

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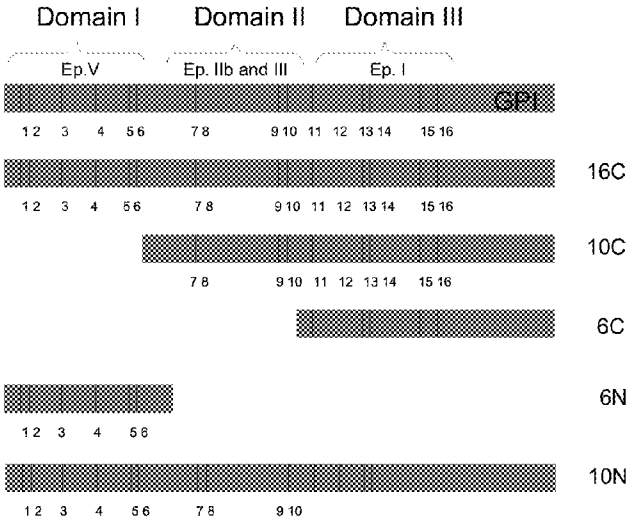


Figure 1

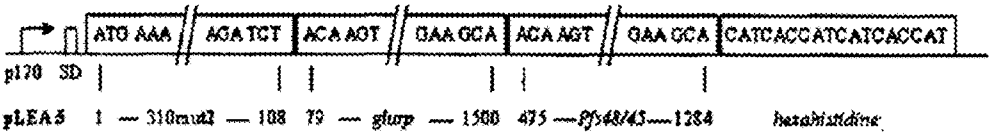
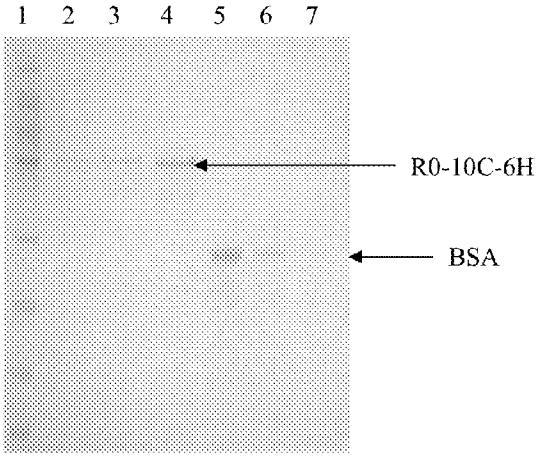


Figure 2.



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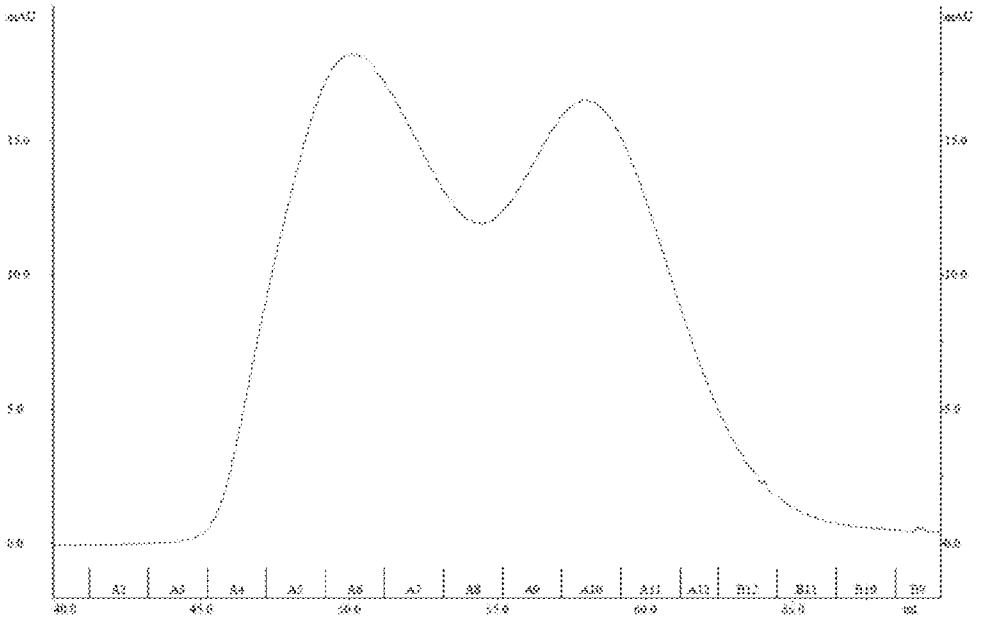

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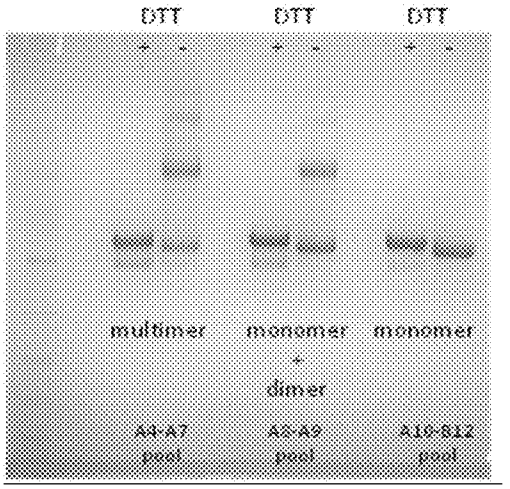

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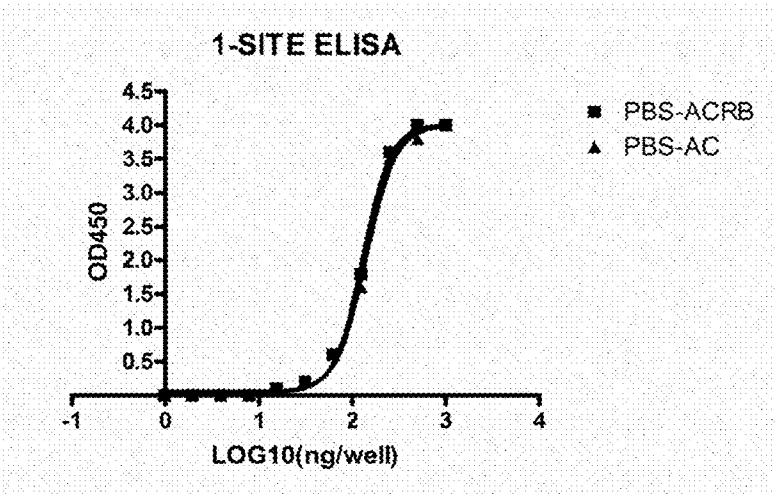

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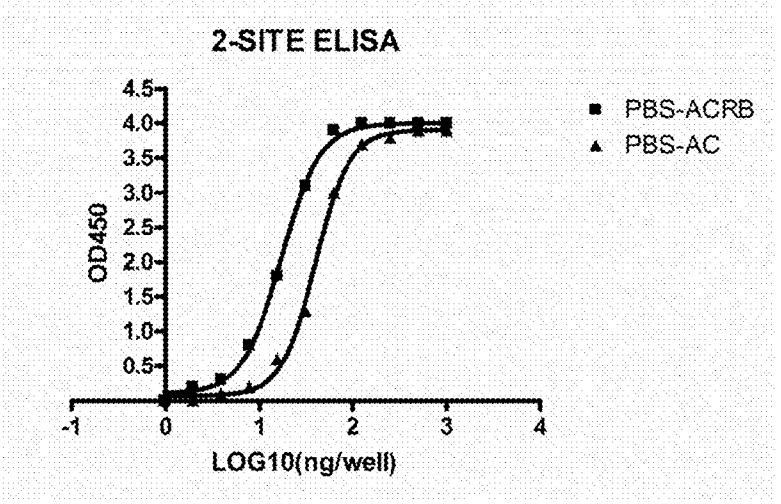

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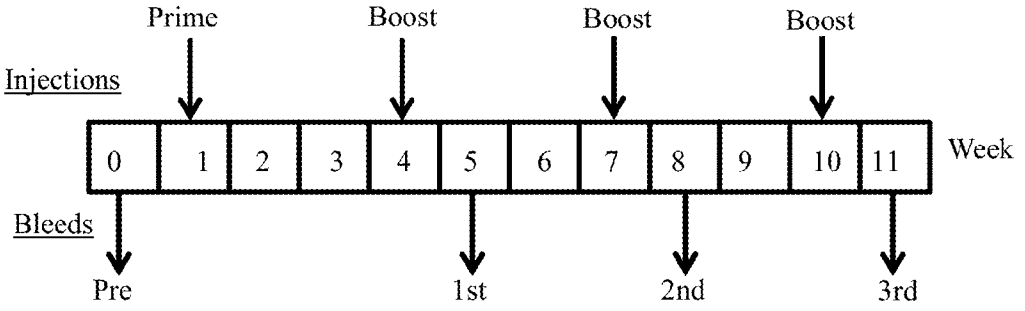

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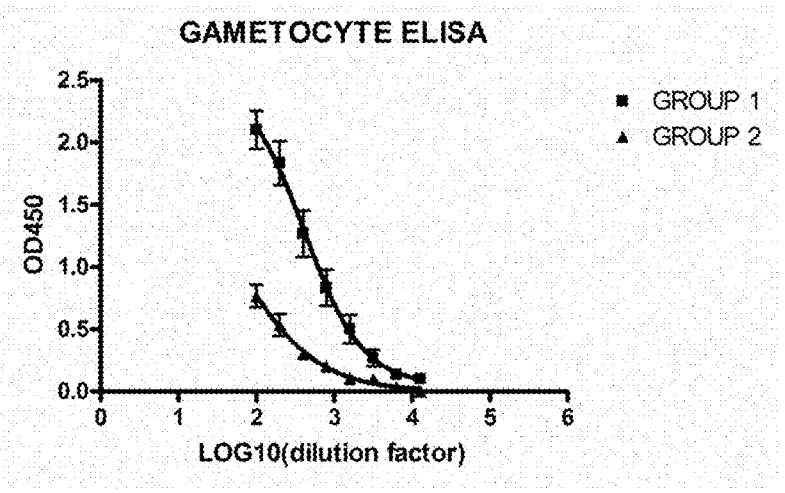

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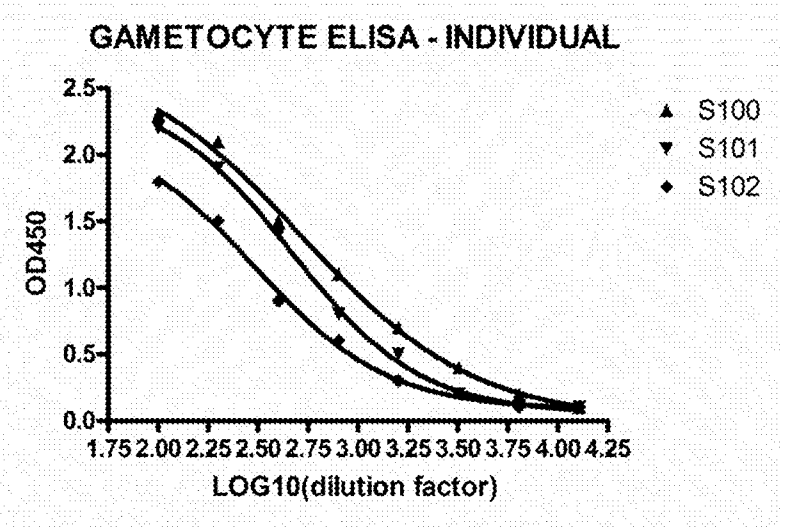

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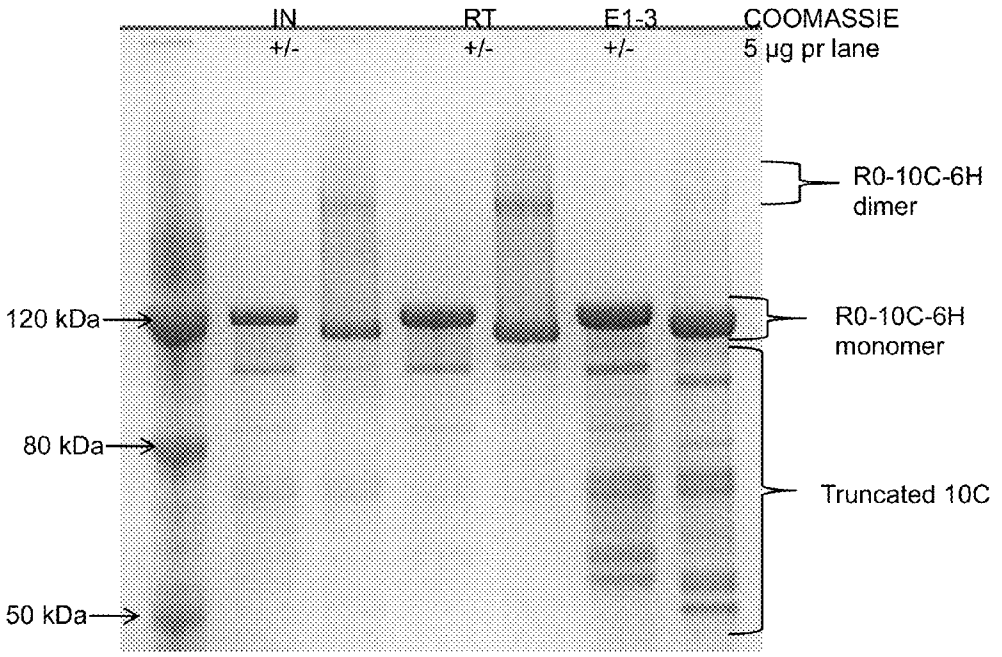

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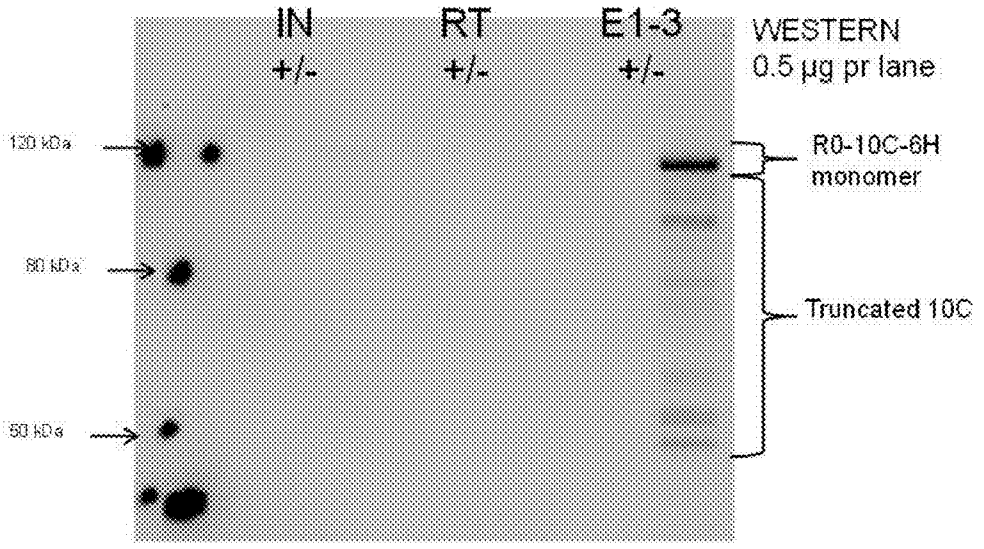

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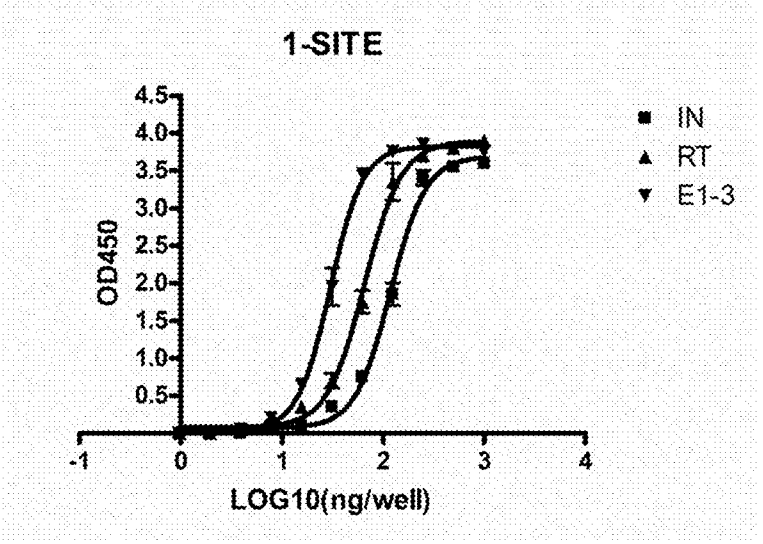

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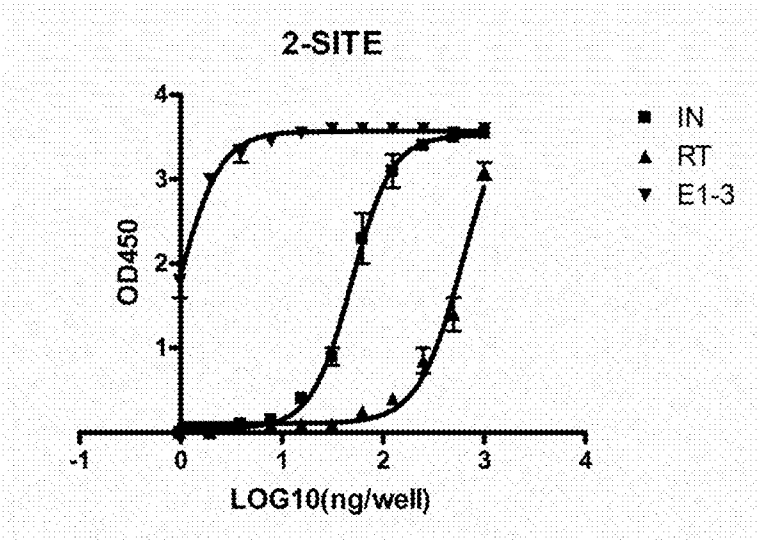

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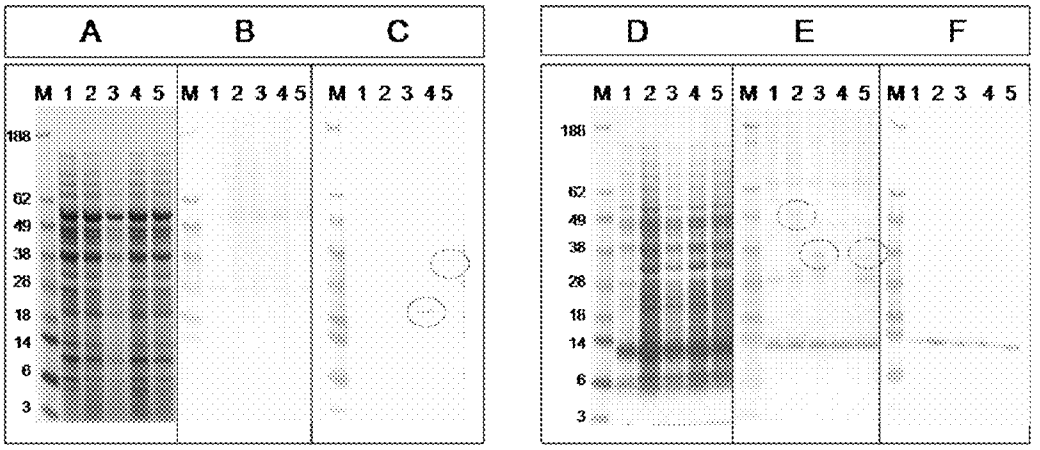

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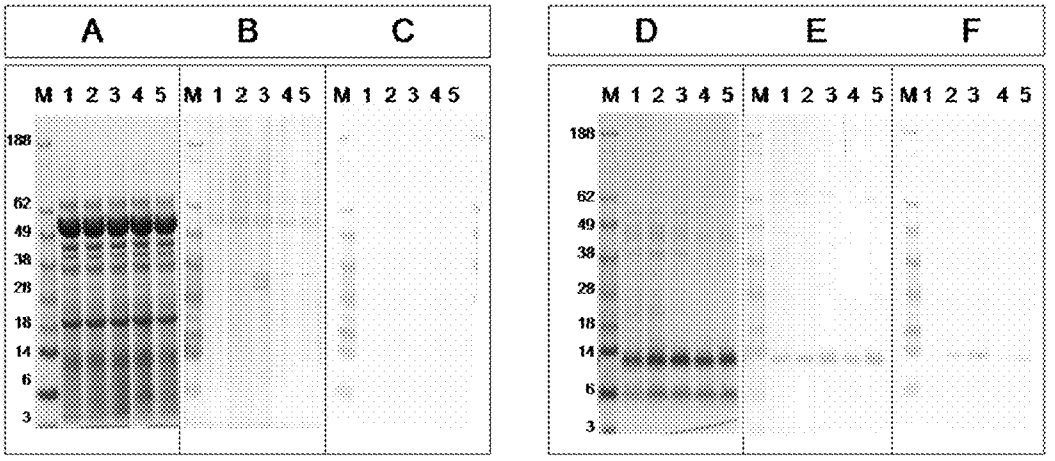
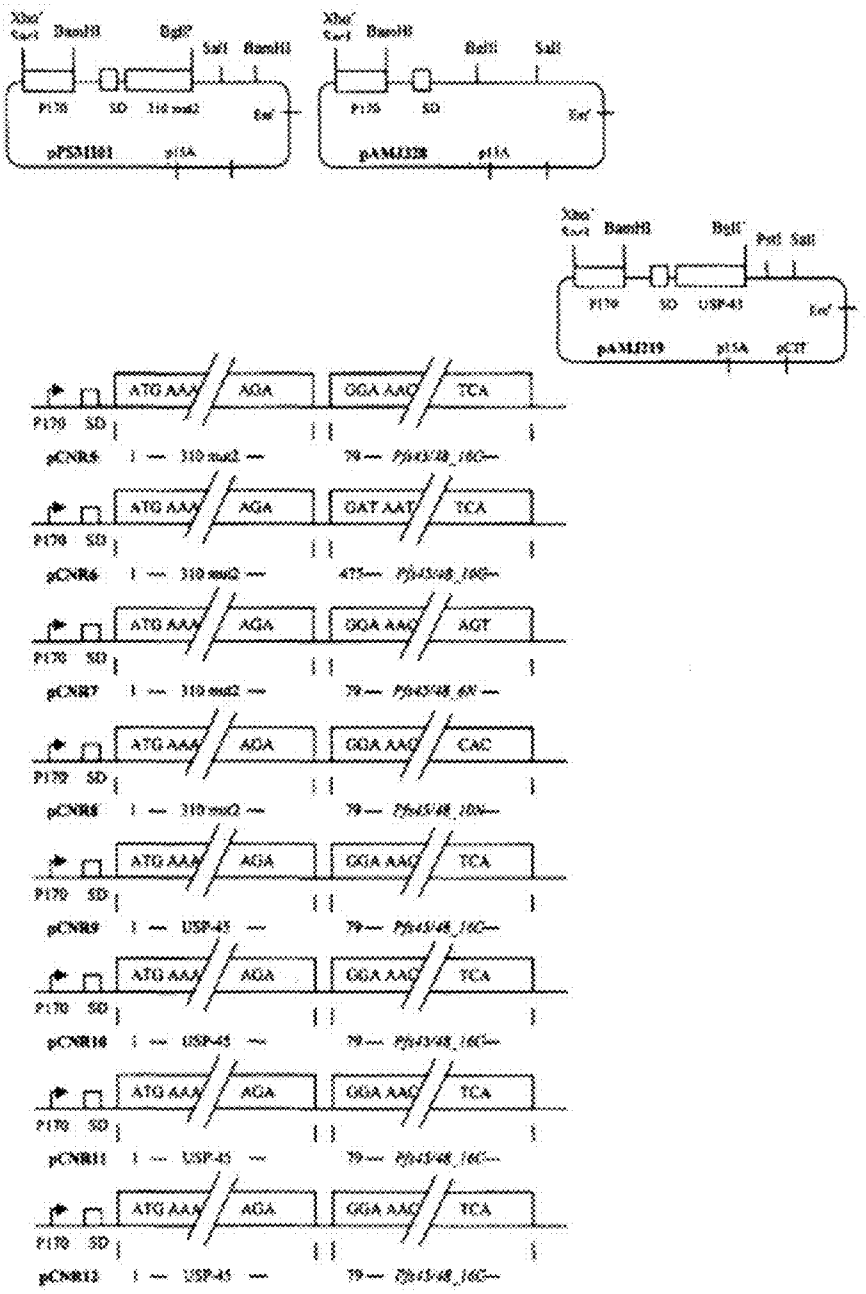


Figure 16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BamHI
BglII
SalI
BamHI
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SD
USP-45
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pCNR7
pCNR8
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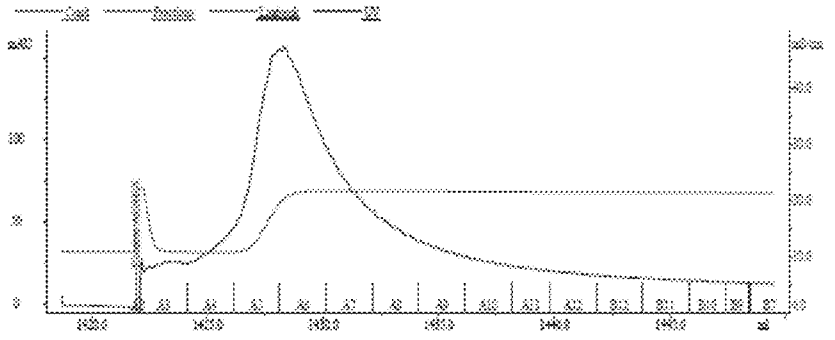
AGA
GGA AAG
TCA
GAT AAT
AGT
CAC

Figure 17

(A)



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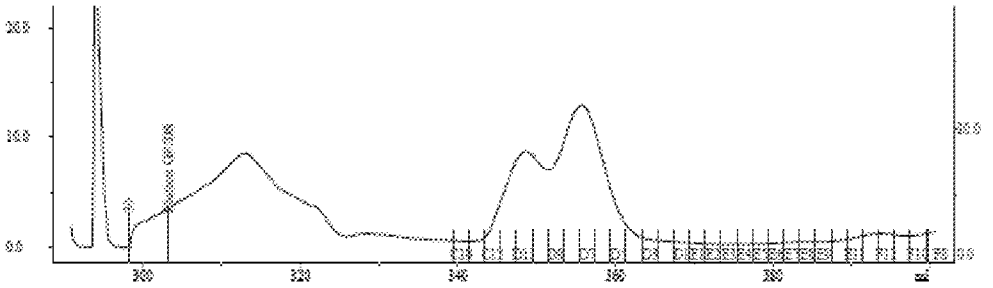

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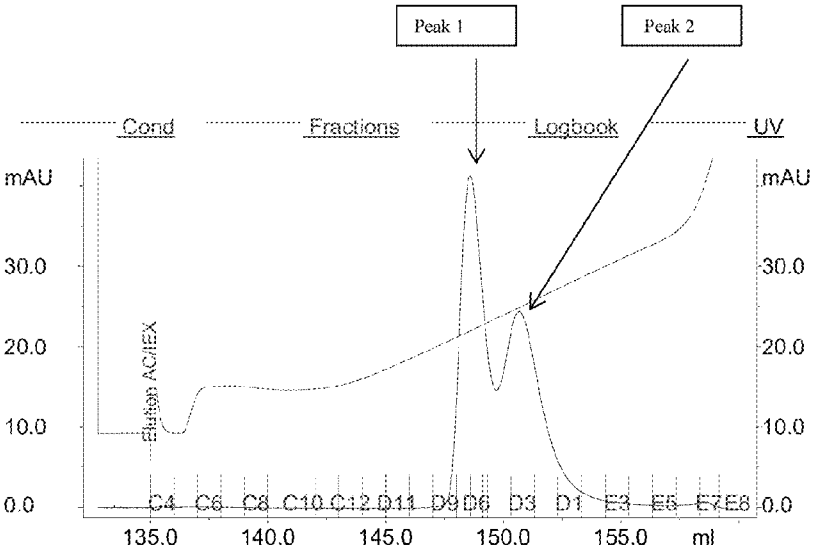

Figure 18

PRODUCTION OF A CYSTEINE RICH PROTEIN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national stage of International Patent Application No. PCT/DK2012/000108, filed Oct. 3, 2013, which claims the benefit of the priority of Danish Patent Application No. PA 2011 00765, tiled Oct. 4, 2011, all of which are incorporated by reference herein.

FIELD OF INVENTION

Large scale production method of a cysteine-rich protein (CYRP) in a lactic acid bacterium by enhancing the secretion by fusion to a glutamate rich protein, stabilizing the monomeric protein, and enhancing the protein folding is described. A cysteine rich antigen based transmission-blocking vaccine or immunogenic composition against malaria comprising fusion proteins derived from *Plasmodium falciparum* Glutamate-rich protein (GLURP) genetically coupled to at least one other *Plasmodium falciparum* CYRP, e.g. Pfs48/45 and the DNA encoding this fusion protein is disclosed.

BACKGROUND

Malaria is affecting 40% of the world's population with an estimated 1.5-2.7 million deaths annually (32). This represents a tremendous human suffering and a burden that prevents the development of the affected endemic communities. Malaria is now almost confined to the poorest tropical areas of Africa, Asia and Latin America, but transmission is being reintroduced to areas where it had previously been eradicated. Malaria is one of the world's greatest public health problems.

The increasing emerging of insecticide resistant vectors and drug resistant parasites calls for investment in new and better control tools. Malaria vaccines hold the potential to dramatically alleviate the burden of malaria. However, our understanding of the mechanisms underlying protective immunity is incomplete hence specific markers of protection still needs to be defined.

An effective malaria vaccine will require the induction of appropriate humoral and cellular immune responses, against several key parasite antigens expressed during the various stages of the parasite life cycle. Each stage in the life cycle provides an opportunity for a vaccine.

Presently, three main lines of malaria vaccine research dominate: (i) induction of immunity against pre-erythrocytic antigens, a strategy rooted in first experiments with UV-inactivated *P. gallinaceum* sporozoites (25), (ii) identification of antigens that induce antibodies with specificities similar to those of immunoglobulin preparations of semi-immune adults with a therapeutic effect in malaria patients (5), and (iii) induction of transmission-blocking (TB) antibodies against parasite antigens that are expressed in the infected mosquito (11). The first two strategies rely on malaria antigens that induce a protective immune response, and the third strategy on malaria antigens that are essential for sexual development of the parasites in the infected mosquito.

The objective of a transmission-blocking malaria vaccine (TBMV) is to prevent an individual from becoming infected with *Plasmodium* parasites by mosquito bites of the *Anopheles* vector. As a result, the spread of malaria in the population is expected to decrease with subsequent reduction of the disease. TBMVs are based on sexual- or sporogonic-specific antigens and designed to arrest the development of

sporogonic stages inside the mosquito. The specific antibodies generated in the human host are passively ingested together with parasites when mosquitoes take a blood meal and will bind to the parasites thereby preventing progression of their sporogonic development. Once inside the mosquito midgut, gametocytes rapidly emerge from the intracellular red blood cell environment to prepare for fertilization and are directly exposed to hostile immune components of the ingested blood. The sporogonic cycle is biologically the most vulnerable part of the lifecycle because parasite numbers are very low which makes this an attractive target for interventions.

The *Plasmodium falciparum* Pfs48/45 is a sexual stage-specific protein expressed by gametocytes (2, 12) and present on the surface of the sporogonic (macrogametes) stages of the malaria parasites. Pfs48/45 plays a key role in male gamete fertility and zygote formation e.g. parasite fertilization (29) and antibodies which target conformational epitopes of Pfs48/45 prevent fertilization (22, 31). Specific antibodies against Pfs48/45 are present in human sera from endemic areas (23) and correlate with TB activity (4, 23-24, 27).

Five distinct B-cell epitopes (epitope II is subdivided into IIa and IIb) have been defined based on binding studies with a panel of Pfs48/45 specific monoclonal antibodies (24) (FIG. **1**). Epitopes I-III in the C-terminal domain of the protein are conformational and epitope IV is linear. For epitope V in the N-terminal domain, both linear- and conformation-dependent monoclonal antibodies have been described (24). Monoclonal antibodies to epitope I and V block transmission effectively in the membrane feeding assay but monoclonal antibodies of epitope IIb and epitope III were ineffective on their own but able to reduce transmission when used in combination (3, 21, 30).

Pfs48/45 has been produced on recombinant form in different expression systems; however, the major challenges with recombinant Pfs48/45 are that it is very difficult to produce correctly folded protein. Proper folding of many CYRPs, including Pfs48/45, depends on correct formation of disulphide bridges. In eukaryotes the oxidizing environment of the endoplasmic reticulum (ER) provides a milieu for disulphide bonds formation. Prokaryotic organisms such as *Escherichia coli* and *Lactococcus lactis* lack the sophisticated ER machinery of disulphide bond formation. In *Escherichia coli* correct disulphide bonds are formed in the periplasmic space catalyzed by a set of periplasmic oxidoreductases. Accordingly, the C-terminal Pfs48/45 fragment (10C) (FIG. **1**) was produced as a correctly folded protein in the periplasm of *Escherichia coli* when genetically fused to the maltose binding protein (MBP) and co-expressed with four periplasmic folding catalysts, (17). Levels of up to 1 mg/L pure correctly folded material was reported. Such expression levels are insufficient for further up-scaling and GMP production.

It is therefore, desirable to develop a large scale production method for a vaccine based on a recombinant protein, which include Pfs48/45 or other cysteine-rich antigens from *P. falciparum* such as the Pfs25, Pfs47, Pfs230, EBA175 and Var2CSA antigens.

SUMMARY OF THE INVENTION

A method of producing a cysteine-rich protein (CYRP) on a large scale is disclosed. The CYRP is produced in a lactic acid bacteria system where the secretion of the protein is enhanced by fusing to a glutamate rich protein. The production is further optimized by stabilising the monomeric protein formation and the folding of the protein by modifying the

redox conditions of the medium and the buffer solution during the down-stream processing. A transmission-blocking vaccine or immunogenic composition against malaria, which has an improved vaccine-induced antibody response, is produced in this way. The vaccine comprises a fusion protein derived from *Plasmodium falciparum* glutamate-rich protein (GLURP) or part of this genetically coupled to at least one other *Plasmodium falciparum* derived CYRP, e.g. Pfs48/45, Pfs25, Pfs47, Pfs230, EBA175 and Var2CSA or the corresponding nucleotide sequence coding said fusion protein.

DETAILED DISCLOSURE OF THE INVENTION

The present invention discloses a method for large scale production of a cysteine-rich protein (CYRP) where the CYRP is fused to a glutamate rich protein (GLURP, SEQ ID NO 1) or part of this and the fusion protein is produced in a lactic acid bacteria. The preferred lactic acid bacterium for the production is *Lactococcus lactis*.

The production is optimized by stabilizing the formation of monomeric fusion protein and enhancing the folding of the protein by modifying the redox conditions of the medium and the down-stream processing buffer.

Preferably the medium is modified by adding reduced form of a sulfhydryl containing compound such as L-cysteine or DTT or glutathione or TCEP or cysteamine (preferably L-cysteine) to the medium to a concentration of about 5-20 mM preferably about 10 mM.

The preferable method to enhance the folding of the protein is by addition of reduced and oxidized form of a sulfhydryl containing compound such as L-cysteine or DTT or glutathione or TCEP or cysteamine (preferably L-cysteine) to the washing buffer during the down-stream processing. The concentration of the reduced form is 1-10 M preferably about 4 mM and the concentration of the oxidized form is 0, 1-5 mM preferably about 0.4 mM

A preferred CYRP originates from *Plasmodium falciparum* where the cysteine rich protein is chosen from the group of Pfs48/45 (SEQ ID NO 3), Pfs25 (SEQ ID NO 21), Pfs230 (SEQ ID NO 17), Pfs47 (SEQ ID NO 19), EBA175 (SEQ ID NO 13), Var2CSA (SEQ ID NO 15) or members of the PfEMP1, RIFIN, STEVOR protein families or a homologue hereof.

The present invention also discloses an antigen based transmission-blocking vaccine or immunogenic composition against malaria comprising a fusion protein derived from *Plasmodium falciparum* glutamate-rich protein (GLURP) or part of GLURP genetically coupled to at least one other *Plasmodium falciparum* derived CYRP or homologues hereof.

A preferred embodiment of the invention is an immunogenic composition or a vaccine where the protein genetically coupled to GLURP-R0 is derived from Pfs48/45 from *Plasmodium falciparum* with a C-terminal hexahistidine sequence, said fusion protein preferably having the following amino acid sequence R0-10C-6H:

(SEQ ID NO. 5)

```
AERSTSENRNKRIGGPKLRGNVTSNIKFPSDNKGKIIRGSNDKLNKNSE
DVLEQSEKSLVSENVPSGLDIDDIPKESIFIQEDQEGQTHSELNPETSE
HSKDLNNNGSKNESSDIISENNKSNKVQNHFESLSDLELLENSSQDNLD
KDTISTEPFPNQKHKDLQQDLNDEPLEPFPTQIHKDYKEKNLINEEDSE
PFPRQKHKKVDNHNEEKNVFHENGSANGNQGSLKLKSFDEHLKDEKIEN
EPLVHENLSIPNDPIEQILNQPEQETNIQEQLYNEKQNVEEKQNSQIPS
LDLKEPTNEDILPNHNPLENIKQSESEINHVQDHALPKENIIDKLDNQK
EHIDQSQHNINVLQENNINNHQLEPQEKPNIESFEPKNIDSEIILPENV
ETEEIIDDVPSPKHSNHETFEEETSESEHEEAVSEKNAHETVEHEETVS
QESNPEKADNDGNVSQNSNNELNENEFVESEKSEHEADNTEKVISSIEG
RSAMVHVRVLKYPHNILFTNLTNDLFTYLPKTYNESNFVSNVLEVELND
GELFVLACELINKKCFQEGKEKALYKSNKIIYHKNLTIFKAPFYVTSKD
VNTECTCKFKNNNYKIVLKPKYEKKVIHGCNFSSNVSSKHTFTDSLDIS
LVDDSAHISCNVHLSEPKYNHLVGLNCPGDIIPDCFFQVYQPESEELEP
SNIVYLDSQINIGDIEYYEDAEGDDKIKLFGIVGSIPKTTSFTCICKKD
KKSAYMTVTIDSAHHHHHH
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The major epitope for transmission blocking antibodies encoded by the 10C fragment is termed "epitope I" (17). This epitope is located in the C-terminal part of Pfs48/45 and include the distal 6 cysteine residues. It was therefore speculated that protein fusions between GLURP.R0 and smaller fragments of Pfs48/45 which only contain the distal 6 cysteine residues might adopt a more correct protein fold in *L. lactis* as compared to the R0.10C protein fusion containing 10 cysteine residues. We have accordingly produced a protein fusion (R0-6C-6H) which contains the GLURP.R0 region fused in frame to a Pfs48/45 fragment containing the distal 6 cysteine residues. The C-terminus of this fusion protein is identical the C-terminus of the R0.10C hybrid protein.

An equivalent and more preferred embodiment RO-6C-6H:

(SEQ ID NO 25)

```
AERSTSENRNKRIGGPKLRGNVTSNIKFPSDNKGKIIRGSNDKLNKNSE
DVLEQSEKSLVSENVPSGLDIDDIPKESIFIQEDQEGQTHSELNPETSE
HSKDLNNNGSKNESSDIISENNKSNKVQNHFESLSDLELLENSSQDNLD
KDTISTEPFPNQKHKDLQQDLNDEPLEPFPTQIHKDYKEKNLINEEDSE
PFPRQKHKKVDNHNEEKNVFHENGSANGNQGSLKLKSFDEHLKDEKIEN
EPLVHENLSIPNDPIEQILNQPEQETNIQEQLYNEKQNVEEKQNSQIPS
LDLKEPTNEDILPNHNPLENIKQSESEINHVQDHALPKENIIDKLDNQK
EHIDQSQHNINVLQENNINNHQLEPQEKPNIESFEPKNIDSEIILPENV
ETEEIIDDVPSPKHSNHETFEEETSESEHEEAVSEKNAHETVEHEETVS
QESNPEKADNDGNVSQNSNNELNENEFVESEKSEHEARSKPKYEKKVIH
GCNFSSNVSSKHTFTDSLDISLVDDSAHISCNVHLSEPKYNHLVGLNCP
GDIIPDCFFQVYQPESEELEPSNIVYLDSQINIGDIEYYEDAEGDDKIK
LFGIVGSIPKTTSFTCICKKDKKSAYMTVTIDSARSHHHHHH
```

It is obvious that the fusion protein as such can comprise the amino acid sequence of GLURP or part hereof coupled to other immunogenic epitopes derived from Pfs48/45 or other cysteine rich proteins derived from *Plasmodium falciparum*, such as Pfs25, Pfs230, Pfs47, EBA175, Var2CSA (Table 1) or members of the PfEMP1, RIFIN, STEVOR protein families or a homologue hereof (17).

The fusion protein can even comprise other proteins derived from *Plasmodium falciparum*, to achieve an addi-

tional immunogenic response. Using MSP3 or part of MSP3 as a fusion partner to GLURP-R0 even enhances the production of the CYRP. A most preferred embodiment to increase the production yield of the CYRP the selected fragment of Pfs48/45 containing 6 cysteine residues (6C) is coupled to GLURP-R0 fused to MSP3 (R0-MSP3-6C-6H):

(SEQ ID NO 27)

AERSTSENRNKRIGGPKLRGNVTSNIKFPSDNKGKIIRGSNDKLNKNSE

DVLEQSEKSLVSENVPSGLDIDDIPKESIFIQEDQEGQTHSELNPETSE

HSKDLNNNGSKNESSDIISENNKSNKVQNHFESLSDLELLENSSQDNLD

KDTISTEPFPNQKHKDLQQDLNDEPLEPFPTQIHKDYKEKNLINEEDSE

PFPRQKHKKVDNHNEEKNVFHENGSANGNQGSLKLKSFDEHLKDEKIEN

EPLVHENLSIPNDPIEQILNQPEQETNIQEQLYNEKQNVEEKQNSQIPS

LDLKEPTNEDILPNHNPLENIKQSESEINHVQDHALPKENIIDKLDNQK

EHIDQSQHNINVLQENNINNHQLEPQEKPNIESFEPKNIDSEIILPENV

ETEEIIDDVPSPKHSNHETFEEETSESEHEEAVSEKNAHETVEHEETVS

QESNPEKADNDGNVSQNSNNELNENEFVESEKSEHEARSKTKEYAEKAK

NAYEKAKNAYQKANQAVLKAKEASSYDYILGWEFGGGVPEHKKEENMLS

HLYVSSKDKENISKENDDVLDEKEEEAEETEEEELERSKPKYEKKVIHG

CNFSSNVSSKHTFTDSLDISLVDDSAHISCNVHLSEPKYNHLVGLNCPG

DIIPDCFFQVYQPESEELEPSNIVYLDSQINIGDIEYYEDAEGDDKIKL

FGIVGSIPKTTSFTCICKKDKKSAYMTVTIDSARSHHHHHH

In another aspect, the invention relates a nucleic acid encoding the above mentioned fusion protein and the use of said nucleic acid for preparing a vaccine composition.

A preferred embodiment of a nucleic acid used for production of a CYRP is the following sequence for R0-10C-6H:

(SEQ ID NO 6)

ATGAAATTTAATAAAAAAAGAGTTGCAATAGCCACGTTTATTGCTTTGA

TATTTGTAAGTTTTTTTACAATATCATCAATCCAAGATGCTCAAGCAGC

CGAAAGATCTACAAGTGAGAATAGAAATAAACGAATCGGGGGTCCTAAA

TTAAGGGGTAATGTTACAAGTAATATAAAGTTCCCATCAGATAACAAAG

GTAAAATTATAAGAGGTTCGAATGATAAACTTAATAAAAACTCTGAAGA

TGTTTTAGAACAAAGCGAAAAATCGCTTGTTTCAGAAAATGTTCCTAGT

GGATTAGATATAGATGATATCCCTAAAGAATCTATTTTTATTCAAGAAG

ATCAAGAAGGTCAAACTCATTCTGAATTAAATCCTGAAACATCAGAACA

TAGTAAAGATTTAAATAATAATGGTTCAAAAAATGAATCTAGTGATATT

ATTTCAGAAAATAATAAATCAAATAAAGTACAAAATCATTTTGAATCAT

TATCAGATTTAGAATTACTTGAAAATTCCTCACAAGATAATTTAGACAA

AGATACAATTTCAACAGAACCTTTTCCTAATCAAAAACATAAAGACTTA

CAACAAGATTTAAATGATGAACCTTTAGAACCCTTTCCTACACAAATAC

ATAAAGATTATAAAGAAAAAAATTTAATAAATGAAGAAGATTCAGAACC

ATTTCCCAGACAAAAGCATAAAAAGGTAGACAATCATAATGAAGAAAAA

AACGTATTTCATGAAAATGGTTCTGCAAATGGTAATCAAGGAAGTTTGA

-continued

AACTTAAATCATTCGATGAACATTTAAAAGATGAAAAAATAGAAAATGA

ACCACTTGTTCATGAAAATTTATCCATACCAAATGATCCAATAGAACAA

ATATTAAATCAACCTGAACAAGAAACAAATATCCAGGAACAATTGTATA

ATGAAAAACAAAATGTTGAAGAAAAACAAAATTCTCAAATACCTTCGTT

AGATTTAAAAGAACCAACAAATGAAGATATTTTACCAAATCATAATCCA

TTAGAAAATATAAAACAAAGTGAATCAGAAATAAATCATGTACAAGATC

ATGCGCTACCAAAAGAGAATATAATAGACAAACTTGATAATCAAAAAGA

ACACATCGATCAATCACAACATAATATAAATGTATTACAAGAAAATAAC

ATAAACAATCACCAATTAGAACCTCAAGAGAAACCTAATATTGAATCGT

TTGAACCTAAAAATATAGATTCAGAAATTATTCTTCCTGAAAATGTTGA

AACAGAAGAAATAATAGATGATGTGCCTTCCCCTAAACATTCTAACCAT

GAAACATTTGAAGAAGAAACAAGTGAATCTGAACATGAAGAAGCCGTAT

CTGAAAAAAATGCCCACGAAACTGTCGAACATGAAGAAACTGTGTCTCA

AGAAAGCAATCCTGAAAAAGCTGATAATGATGGAAATGTATCTCAAAAC

AGCAACAACGAATTAAATGAAAATGAATTCGTTGAATCGGAAAAAAGCG

AGCATGAAGCAGATAATACTGAAAAGGTTATATCAAGTATAGAAGGGAG

AAGTGCTATGGTACATGTACGTGTATTAAAATATCCACATAATATTTTA

TTTACTAATTTAACAAATGATCTTTTTACATATTTGCCGAAAACATATA

ATGAATCTAATTTTGTAAGTAATGTATTAGAAGTAGAATTGAATGATGG

AGAATTATTTGTTTTAGCTTGTGAACTAATTAATAAAAAATGTTTTCAA

GAAGGAAAAGAAAAAGCCTTATATAAAAGTAATAAAATAATTTATCATA

AAAACTTAACTATCTTTAAAGCTCCATTTTATGTTACATCAAAAGATGT

TAATACAGAATGTACATGCAAATTTAAAAATAATAATTATAAAATAGTT

TTAAAACCAAAATATGAAAAAAAAGTCATACACGGATGTAACTTCTCTT

CAAATGTTAGTTCTAAACATACTTTTACAGATAGTTTAGATATTTCTTT

AGTTGATGATAGTGCACATATTTCATGTAACGTACATTTGTCTGAACCA

AAATATAATCATTTGGTAGGTTTAAATTGTCCTGGTGATATTATACCAG

ATTGCTTTTTTCAAGTATATCAACCTGAATCAGAAGAACTTGAACCATC

CAACATTGTTTATTTAGATTCACAAATAAATATAGGAGATATTGAATAT

TATGAAGATGCTGAAGGAGATGATAAAATTAAATTATTTGGTATAGTTG

GAAGTATACCAAAAACGACATCTTTTACTTGTATATGTAAGAAGGATAA

AAAAAGTGCTTATATGACAGTTACTATAGATTCAGCACATCACCATCAT

CACCATTAG

And the nucleic acid sequence for R0-6C-6H:

(SEQ ID NO 26)

ATGAAATTTAATAAAAAAAGAGTTGCAATAGCCACGTTTATTGCTTTGAT

ATTTGTAAGTTTTTTTACAATATCATCAATCCAAGATGCTCAAGCAGCCG

AAAGATCCACAAGTGAGAATAGAAATAAACGAATCGGGGGTCCTAAATTA

AGGGGTAATGTTACAAGTAATATAAAGTTCCCATCAGATAACAAAGGTAA

AATTATAAGAGGTTCGAATGATAAACTTAATAAAAACTCTGAAGATGTTT

-continued

TAGAACAAAGCGAAAAATCGCTTGTTTCAGAAAATGTTCCTAGTGGATTA

CTCAGATATAGATGATATCCCTAAAGAATCTATTTTTATTCAAGAAGATC

AAGAAGGTCAAATTCTGAATTAAATCCTGAAACATCAGAACATAGTAAAG

ATTTAAATAATAATGGTTCAAAAAATGAATCTAGTGATATTATTTCAGAA

AATAATAAATCAAATAAAGTACAAAATCATTTTGAATCATTATCAGATTT

AGAATTACTTGAAAATTCCTCACAAGATAATTTAGACAAAGATACAATTT

CAACAGAACCTTTTCCTAATCAAAAACATAAAGACTTACAACAAGATTTA

AATGATGAACCTTTAGAACCCTTTCCTACACAAATACATAAAGATTATAA

AGAAAAAAATTTAATAAATGAAGAAGATTCAGAACCATTTCCCAGACAAA

AGCATAAAAAGGTAGACAATCATAATGAAGAAAAAAACGTATTTCATGAA

AATGGTTCTGCAAATGGTAATCAAGGAAGTTTGAAACTTAAATCATTCGA

TGAACATTTAAAAGATGAAAAAATAGAAAATGAACCACTTGTTCATGAAA

ATTTATCCATACCAAATGATCCAATAGAACAAATATTAAATCAAAAAACA

CCTGAACAAGAAACAAATATCCAGGAACAATTGTATAATGAAAAACAAAA

TGTTGAAGAAAATTCTCAAATACCTTCGTTAGATTTAAAAGAACCAACAA

ATGAAGATATTTTACCAAATCATAATCCATTAGAAAATATAAAACAAAGT

GAATCAGAAATAAATCATGTACAAGATCATGCGCTACCAAAAGAGAATAT

AATAGACAAACTTGATAATCAAAAAGAACACATCGATCAATCACAACATA

ATATAAATGTATTACAAGAAAATAACATAAACAATCACCAATTAGAACCT

CAAGAGAAACCTAATATTGAATCGTTTGAACCTAAAAATATAGATTCAGA

AATTATTCTTCCTGAAAATGTTGAAACAGAAGAAATAATAGATGATGTGC

CTTCCCCTAAACATTCTAACCATGAAACATTTGAAGAAGAAACAAGTGAA

TCTGAACATGAAGAAGCCGTATCTGAAAAAAATGCCCACGAAACTGTCGA

ACATGAAGAAACTGTGTCTCAAGAAAGCAATCCTGAAAAAGCTGATAATG

ATGGAAATGTATCTCAAAACAGCAACAACGAATTAAATGAAAATGAATTC

GTTGAATCGGAAAAAAGCGAGCATGAAGCAAGATCCGAAAAAAAAGTCAT

ACACGGATGTAACTTCTCTTCAAATGTTAGTTCTAAACATACTTTTACAG

ATAGTTTAGATATTTCTTTAGTTGATGATAGTGCACATATTTCATGTAAC

GTACATTTGTCTGAACCAAAATATAATCATTTGGTAGGTTTAAATTGTCC

TGGTGATATTATACCAGATTGCTTTTTTCAAGTATATCAACCTGAATCAG

AAGAACTTGAACCATCCAACATTGTTTATTTAGATTCACAAATAAATATA

GGAGATATTGAATATTATGAAGATGCTGAAGGAGATGATAAAATTAAATT

ATTTGGTATAGTTGGAAGTATACCAAAAACGACATCTTTTACTTGTATAT

GTAAGAAGGATAAAAAAAGTGCTTATATGACAGTTACTATAGATTCAGCA

AGATCTCATCACCATCATCACCATTAG

The nucleic acid sequence for GLURP-R0-MSP3-6C-6H:

(SEQ ID NO 28)

ATGAAATTTAATAAAAAAAGAGTTGCAATAGCCACGTTTATTGCTTTGAT

ATTTGTAAGTTTTTTTACAATATCATCAATCCAAGATGCTCAAGCAGCCG

AAAGATCCACAAGTGAGAATAGAAATAAACGAATCGGGGGTCCTAAATTA

-continued

AGGGGTAATGTTACAAGTAATATAAAGTTCCCATCAGATAACAAAGGTAA

AATTATAAGAGGTTCGAATGATAAACTTAATAAAAACTCTGAAGATGTTT

TAGAACAAAGCGAAAAATCGCTTGTTTCAGAAAATGTTCCTAGTGGATTA

GATATAGATGATATCCCTAAAGAATCTATTTTTATTCAAGAAGATCAAGA

AGGTCAAACTCATTCTGAATTAAATCCTGAAACATCAGAACATAGTAAAG

ATTTAAATAATAATGGTTCAAAAAATGAATCTAGTGATATTATTTCAGAA

AATAATAAATCAAATAAAGTACAAAATCATTTTGAATCATTATCAGATTT

AGAATTACTTGAAAATTCCTCACAAGATAATTTAGACAAAGATACAATTT

CAACAGAACCTTTTCCTAATCAAAAACATAAAGACTTACAACAAGATTTA

AATGATGAACCTTTAGAACCCTTTCCTACACAAATACATAAAGATTATAA

AGAAAAAAATTTAATAAATGAAGAAGATTCAGAACCATTTCCCAGACAAA

AGCATAAAAAGGTAGACAATCATAATGAAGAAAAAAACGTATTTCATGAA

AATGGTTCTGCAAATGGTAATCAAGGAAGTTTGAAACTTAAATCATTCGA

TGAACATTTAAAAGATGAAAAAATAGAAAATGAACCACTTGTTCATGAAA

ATTTATCCATACCAAATGATCCAATAGAACAAATATTAAATCAACCTGAA

CAAGAAACAAATATCCAGGAACAATTGTATAATGAAAAACAAAATGTTGA

AGAAAAACAAAATTCTCAAATACCTTCGTTAGATTTAAAAGAACCAACAA

ATGAAGATATTTTACCAAATCATAATCCATTAGAAAATATAAAACAAAGT

GAATCAGAAATAAATCATGTACAAGATCATGCGCTACCAAAAGAGAATAT

AATAGACAAACTTGATAATCAAAAAGAACACATCGATCAATCACAACATA

ATATAAATGTATTACAAGAAAATAACATAAACAATCACCAATTAGAACCT

CAAGAGAAACCTAATATTGAATCGTTTGAACCTAAAAATATAGATTCAGA

AATTATTCTTCCTGAAAATGTTGAAACAGAAGAAATAATAGATGATGTGC

CTTCCCCTAAACATTCTAACCATGAAACATTTGAAGAAGAAACAAGTGAA

TCTGAACATGAAGAAGCCGTATCTGAAAAAAATGCCCACGAAACTGTCGA

ACATGAAGAAACTGTGTCTCAAGAAAGCAATCCTGAAAAAGCTGATAATG

ATGGAAATGTATCTCAAAACAGCAACAACGAATTAAATGAAAATGAATTC

GTTGAATCGGAAAAAAGCGAGCATGAAGCAAGATCCAAAACAAAAGAATA

TGCTGAAAAAGCAAAAAATGCTTATGAAAAGGCAAAAAATGCTTATCAAA

AAGCAAACCAAGCTGTTTTAAAAGCAAAAGAAGCTTCTAGTTATGATTAT

ATTTTAGGTTGGGAATTTGGAGGAGGCGTTCCAGAACACAAAAAAGAAGA

AAATATGTTATCACATTTATATGTTTCTTCAAAGGATAAGGAAAATATAT

CTAAGGAAAATGATGATGTATTAGATGAGAAGGAAGAAGAGGCAGAAGAA

ACAGAAGAAGAAGAACTTGAAAGATCCGAAAAAAAAAGTCATACACGGATG

TAACTTCTCTTCAAATGTTAGTTCTAAACATACTTTTACAGATAGTTTAG

ATATTTCTTTAGTTGATGATAGTGCACATATTTCATGTAACGTACATTTG

TCTGAACCAAAATATAATCATTTGGTAGGTTTAAATTGTCCTGGTGATAT

TATACCAGATTGCTTTTTTCAAGTATATCAACCTGAATCAGAAGAACTTG

AACCATCCAACATTGTTTATTTAGATTCACAAATAAATATAGGAGATATT

GAATATTATGAAGATGCTGAAGGAGATGATAAAATTAAATTATTTGGTAT

AGTTGGAAGTATACCAAAAACGACATCTTTTACTTGTATATGTAAGAAGG

-continued

ATAAAAAAAGTGCTTATATGACAGTTACTATAGATTCAGCAAGATCTCAT

CACCATCATCACCATTAG

TABLE 1

SEQ ID 1	GLURP protein sequence
SEQ ID 2	GLURP nucleic acid sequence
SEQ ID 3	Pfs48/45 protein sequence
SEQ ID 4	Pfs48/45 nucleic acid sequence
SEQ ID 5	RO-10C-6H protein sequence
SEQ ID 6	RO-10C-6H nucleic acid sequence
SEQ ID 7	RO-16C-6H protein sequence
SEQ ID 8	RO-16C-6H nucleic acid sequence
SEQ ID 9	tRO-10C protein sequence
SEQ ID 10	tRO-10C nucleic acid sequence
SEQ ID 11	tR0-16C protein sequence
SEQ ID 12	tR0-16C nucleic acid sequence
SEQ ID 13	EBA175 protein sequence
SEQ ID 14	EBA175 nucleic acid sequence
SEQ ID 15	Var2CSA protein sequence
SEQ ID 16	Var2CSA nucleic acid sequence
SEQ ID 17	Pfs230 protein sequence
SEQ ID 18	Pfs230 nucleic acid sequence
SEQ ID 19	Pfs47 protein sequence
SEQ ID 20	Pfs47 nucleic acid sequence
SEQ ID 21	Pfs25 protein sequence
SEQ ID 22	Pfs25 nucleic acid sequence
SEQ ID 23	MSP3 protein sequence
SEQ ID 24	MSP3 nucleic acid sequence
SEQ ID 25	RO-6C-6H protein sequence
SEQ ID 26	RO-6C-6H nucleic acid sequence
SEQ ID 27	RO-MSP3-6C-6H protein sequence
SEQ ID 28	RO-MSP3-6C-6H nucleic acid seq.

Since *Lactococcus lactis* lack the sophisticated ER machinery of disulphide bond formation we speculated that *Lactococcus lactis* being very cysteine poor in its proteome and lacking any disulphide assisting machinery would be unsuited for production of CYRPs like Pfs48/45 either because of instability of the protein or from an insufficient amount of tRNA for cystein leading to translational problems and premature termination of transcription and/or translation. However, contrary to expectations we found surprising high levels of expression of correctly folded Pfs48/45 in *Lactococcus lactis* when this protein was genetically linked to the N-terminal region of GLURP.

Since vaccines based on GLURP and Pfs48/45 induce IgG antibody responses with different in vitro activities and possibly complement each other as targets for the immune system, the $GLURP_{133-500}$ region (termed tR0) was fused to both the $Pfs48/45_{27-417}$ region (termed 16C) creating the recombinant fusion protein tR0-16C and the $Pfs48/45_{159-428}$ region (termed 10C) regions creating the recombinant fusion protein tR0-10C. These two constructs were introduced in *Lactococcus lactis* in a gene expression system, which is based on the pH and growth phase regulated promoter, P170, from *Lactococcus lactis* (1, 9, 16). This gene expression system offers a simple fermentation procedure, which has been developed specifically for the P170 promoter.

Lactococcus lactis was chosen as expression host because i) it is a well characterized industrial generally recognized as safe (GRAS) microorganism, best known for its use in the production of fermented dairy products, ii) it can be grown in a defined synthetic medium, iii) it does not produce toxic substances and iv) it has the possibility of secretory protein expression, which offers easy recovery of target protein with the added advantage of optimizing growth conditions for preservation of target protein activity and stability.

The tR0 region of GLURP and the 16C or the 10C region of Pfs48/45 have now been produced, as the hybrid proteins, tR0-16C and tR0-10C using *Lactococcus lactis*, with estimated expression levels of up to 50 mg fusion protein pr. liter culture supernatant. To facilitate purification a C-terminal hexahistidine (6H) was introduced in each construct leading to constructs termed tR0-16C-6H and tR0-10C-6H, respectively. Following addition of 6H the tR0 was changed to the $GLURP_{27-500}$ region (termed R0). Both permutations didn't influence the protein expression levels.

In contrast, when either of the 16C or 10C regions of Pfs48/45 were cloned individually into the same *Lactococcus lactis* expression plasmid without the GLURP fusion partner, protein yields were low, and the recombinant proteins rPfs45/48_16C, rPfs45/48_10C seemed to remain inside the cell indicating little or no secretion.

Thus, R0 helps in both cases to increases expression levels of these otherwise non-secreted 16C and 10C protein fragments. Moreover, R0 also helps to increase the yield of correctly folded Pfs48/45 protein species in the culture supernatant as determined by the reactivity with mAb 85RF45.1 which possesses strong TB activity and is specific for the conformational epitope I. This is a surprising ability of R0 which can be used with other malaria antigens also.

When R0-10C-6H and R0-16C-6H are produced, the majority (>60%) of the protein is produced as aggregates of disulphide bonded monomers, as judged from a non-reducing SDS-PAGE gel. The monomeric form is stabilized by modifying the redox potential of the medium by the addition of L-cysteine, dithiothreitol (DTT), reduced glutathione (GSH) or tris(2-carboxyethyl)phosphine (TCEP) in the range of 1-20 mM, making the monomer fraction >50%.

The monomeric protein can be separated from the aggregates using gel filtration. Immunoreactivity of these monomeric species using a set of monoclonal antibodies targeting epitope I, IIb and III (FIG. **1**) is very low, which indicates uncorrect cysteine pairing in the monomer. The correct cysteine pairing of R0-10C-6H can be achieved by modifying the redox potential of the buffer by the addition of reduced and oxidized glutathione or cysteine or cysteamine or DTT or TCEP to the washing buffer in the range of 1-10 and 0.1-5, respectively during the initial immobilized metal-ion affinity chromatography (IMAC) capturing step. This treatment leads to a change in the immunoreactivity towards the beforementioned monoclonal antibodies. This change of the monomeric R0-10C-6H hybrid protein have been studied in rats with Freunds complete/incomplete adjuvant. Three rats received R0-10C-6H purified without glutathione ($R0\text{-}10C\text{-}6H_{-GSH}$) and three rats received R0-10C-6H purified with glutathione ($R0\text{-}10C\text{-}6H_{+GSH}$). When the sera from the rats where tested in an ELISA against native Pfs48/45 extracted from gametocytes, the three $R0\text{-}10C\text{-}6H_{-GSH}$ rat sera almost didn't respond, while the three $R0\text{-}10C\text{-}6H_{+GSH}$ rat sera responded well. One out of the three $R0\text{-}10C\text{-}6H_{+GSH}$ rat sera demonstrated >90% transmission blocking activity.

In another embodiment of this invention, fragments of Pfs48/45 are fused in-frame to GMZ2, a protein fusion between GLURP.R0 and MSP3, thus creating R0.MSP3.10C or R0.MSP3.6C chimera. These alternative versions of Pfs48/45 aim to beside the main objective of increasing the yield of correctly folded protein species in the culture supernatant of *L. lactis*, to expand the breath of the immune response against *P. falciparum* by including responses against one (GLURP.R0) or two (GLURP.R0 and MSP3 antigens from the blood stage of the infection, and at the same time potentially enhance antibody responses against correctly folded epitope I of Pfs48/45.

The GLURP-Pfs48/45 hybrid protein secreted in the *Lactococcus lactis* or in another lactic acid bacteria expression system under controlled medium redox potential and purified under controlled buffer redox potential, therefore has four major advantages compared to the Pfs48/45 molecule alone:

i) GLURP enhance secretion of Pfs48/45

ii) Medium redox potential stabilizes formation of monomeric Pfs48/45

iii) Buffer redox potential enhances proper folding of Pfs48/45.

iv) The fusion protein elicits antibodies that target the sexual as well as the a-sexual stages of *Plasmodium falciparum.*

Definitions

By monomeric form is meant a protein species with the molecular weight determined by mass spectroscopy to be equal to the molecular weight of the protein as calculated from the amino acid sequence of the protein.

By multimeric form is meant a protein species with the molecular weight determined by mass spectroscopy to be equal to two times or more of the molecular weight of the monomeric form. Under reducing conditions the multimeric and monomeric forms are the same.

By correctly folded monomeric form is meant the monomeric form protein species which has correct disulphides as determined by conformational monoclonal antibodies.

By conformational monoclonal antibodies is meant antibodies originating from a immortalized single B-cell line and which can detect correctly folded monomeric form of protein in a Western blot or ELISA under nonreducing conditions, but not under reducing conditions.

By controlled medium redox potential is meant the addition of reduced forms of L-cysteine or DTT or glutathione or TCEP or cysteamine or any other small sulfhydryl containing compound capable of reducing cystines in proteins in the range of 1-20 mM, preferably 10 mM of L-cysteine to the medium in which the protein production is taking place.

By controlled buffer redox potential is meant the addition of reduced and oxidized forms of L-cysteine or DTT or glutathione or TCEP or cysteamine or any other small sulfhydryl containing compound capable of reducing or oxidixing cystines or cysteines in proteins. Concentrations is in the range of 1-10 mM (of the reduced form) and 0.1-5 mM (of the oxidized form), respectively, preferably 4 mM reduced L-cysteine and 0.4 mM oxidized L-cysteine to a washing buffer during the initial immobilized metal-ion affinity chromatography (IMAC) capturing step. The contact time with the buffer can be between 15 min and 4 hours, but preferably 30 min.

By potency of a given protein sample is meant the value in arbitrary units which comes from division of the EC50 value from a standard 2-SITE ELISA with the EC50 value from a standard 1-SITE ELISA.

By relative potency of a given protein sample is meant the potency of a sample divided by the potency of a reference sample. E.g. if the reference sample is input for a purification step, then the relative potency of an eluted sample equals to fold purification in the given step. If the reference sample is immunopurified sample, the relative potency equals the actual purity of the given sample.

By a glutamate rich protein is meant any protein with more than 10% glutamic acid residues.

By GLURP is meant the glutamate-rich protein from *Plasmodium falciparum* or a fraction of this protein. A preferred fraction is the $GLURP_{27\text{-}500}$ region is termed R0.

By cysteine-rich protein (CYRP) is meant any protein with more than six cysteine residues. Cysteine rich proteins derived from *Plasmodium falciparum* e.g. Pfs45/48, PfEMP1, RIFIN, STEVOR, Pfs230, EBA-175, Pfs25, Pfs47, Var2CSA or immunogenic fragments hereof. Producing full-length CYRP on recombinant form is often difficult due to incorrect protein folding and possibly aggregation as illustrated with our 16C construct. Instead, one may focus on a small fragment of the protein comprising one or several B-cell epitopes, defined as "immunogenic fragments". Examples of preferred fragments of Pfs48/45 are described in example 6 as fragment 10C and 6C. Single amino acid deletions or substitution that does not alter the antibody-binding properties of the epitope can also be beneficial if they results in a more correct folding of the polypeptide fragment and a more favorable presentation to the immune system.

By homologues are meant polypeptides or polypeptide fragments where single amino acid deletions or substitutions of the fragment that do not alter the immunogenic properties of the epitope have been introduced or various length of a fragment that does not alter the immunogenic properties of the epitope. Examples of homologue fragments of Pfs48/45 are described in table 7 in example 6. Another type of homologue can be fragments including amino acids that make up part of a restriction cleaving site e.g. the N-terminal aa AERS in some of the present constructs.

Immunogenic Fragment or Epitope

An immunogenic fraction, fragment or epitope is defined as a part of or a fragment of the protein that induces an immune response in a biological sample or an individual currently or previously infected with a microorganism such as malaria.

The immune response may be monitored by one of the following methods:

An in vitro cellular response is determined by release of a relevant cytokine such as IFN-γ, from lymphocytes withdrawn from an animal or human being currently or previously infected with malaria, or by detection of proliferation of these T cells. The induction being performed by the addition of the polypeptide or the immunogenic portion to a suspension comprising from 1×10^5 cells to 3×10^5 cells per well. The cells being isolated from the blood, the spleen, the liver or the lung and the addition of the polypeptide or the immunogenic portion resulting in a concentration of not more than 20 μg per ml suspension and the stimulation being performed from two to five days. For monitoring cell proliferation the cells are pulsed with radioactive labeled Thymidine and after 16-22 hours of incubation detecting the proliferation by liquid scintillation counting. A positive response being a response more than background plus two standard deviations. The release of IFN-γ can be determined by the ELISA method, which is well known to a person skilled in the art. A positive response being a response more than background plus two standard deviations. Other cytokines than IFN-γ could be relevant when monitoring the immunological response to the polypeptide, such as IL-12, TNF-α, IL-4, IL-5, IL-10, IL-6, TGF-β. Another and more sensitive method for determining the presence of a cytokine (e.g. IFN-γ) is the ELISPOT method where the cells isolated from either the blood, the spleen, the liver or the lung are diluted to a concentration of preferable of 1 to 4×10^6 cells/ml and incubated for 18-22 hrs in the presence of the polypeptide or the immunogenic portion resulting in a concentration of not more than 20 μg per ml. The cell suspensions are hereafter diluted to 1 to 2×10^6/ml and transferred to Maxisorp plates coated with anti-IFN-γ and incubated for preferably 4 to 16 hours. The IFN-γ producing cells are determined by the use of labelled secondary anti-IFN-γ antibody and a relevant substrate

giving rise to spots, which can be enumerated using a dissection microscope. It is also a possibility to determine the presence of mRNA coding for the relevant cytokine by the use of the PCR technique. Usually one or more cytokines will be measured utilizing for example the PCR, ELISPOT or ELISA. It will be appreciated by a person skilled in the art that a significant increase or decrease in the amount of any of these cytokines induced by a specific polypeptide can be used in evaluation of the immunological activity of the polypeptide.

An in vitro cellular response may also be determined by the use of T cell lines derived from an immune individual or a malaria infected person where the T cell lines have been driven with either live *P. falciparum*, extracts from the parasite or culture filtrate for 10 to 20 days with the addition of IL-2. The induction being performed by addition of not more than 20 μg polypeptide per ml suspension to the T cell lines containing from 1×10^5 cells to 3×10^5 cells per well and incubation being performed from two to six days. The induction of IFN-γ or release of another relevant cytokine is detected by ELISA. The stimulation of T cells can also be monitored by detecting cell proliferation using radioactively labeled Thymidine as described above. For both assays a positive response being a response more than background plus two standard deviations.

An in vivo cellular response which may be determined as a positive DTH response after intradermal injection or local application patch of at most 100 μg of the polypeptide or the immunogenic portion to an individual who is clinically or subclinically infected with *P. falciparum*, a positive response having a diameter of at least 5 mm 72-96 hours after the injection or application.

An in vitro humoral response is determined by a specific antibody response in an immune or infected individual. The presence of antibodies may be determined by an ELISA technique or a Western blot where the polypeptide or the immunogenic portion is absorbed to either a nitrocellulose membrane or a polystyrene surface. The serum is preferably diluted in PBS from 1:10 to 1:100 and added to the absorbed polypeptide and the incubation being performed from 1 to 12 hours. By the use of labeled secondary antibodies the presence of specific antibodies can be determined by measuring the OD e.g. by ELISA where a positive response is a response of more than background plus two standard deviations or alternatively a visual response in a Western blot.

Another relevant parameter is measurement of the protection in animal models induced after vaccination with the polypeptide in an adjuvant or after DNA vaccination. Suitable animal models include primates, guinea pigs or mice, which are challenged with an infection. Readout for induced protection could be decrease of the parasite density compared to non-vaccinated animals; prolonged survival times compared to non-vaccinated animals and diminished weight loss compared to non-vaccinated animals.

Homologue Protein

Homology is defined as an analogue or variant of the fusion protein of the present invention. The fusion protein is characterized by specific amino acids and is encoded by specific nucleic acid sequences. It will be understood that such sequences include analogues and variants produced by recombinant or synthetic methods wherein such polypeptide sequences have been modified by substitution, insertion, addition or deletion of one or more amino acid residues in the recombinant polypeptide and still be immunogenic in any of the biological assays described herein. Substitutions are preferably "conservative". Substitutions are preferably silent substitutions in the codon usage which will not lead to any change in the amino acid sequence, but may be introduced to enhance the expression of the protein. These are defined according to the following table. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other. The amino acids in the third column are indicated in one-letter code.

TABLE 2

ALIPHATIC	Non-polar	GAP
		ILV
	Polar-uncharged	CSTM
		NQ
	Polar-charged	DE
		KR
AROMATIC		HFWY

Fusion Proteins

A recombinant fusion protein is encoded by a nucleotide sequence, which is obtained by genetically joining nucleotide sequences derived from different regions of one gene and/or by joining nucleotide sequences derived from two or more separate genes. These nucleotide sequences may be derived from *P. falciparum*, but they may also be derived from other organisms, the plasmids used for the cloning procedures or from other nucleotide sequences. According to the present invention the fusion proteins are produced in a lactic acid bacteria system.

As used herein, the term "lactic acid bacterium" designates a gram-positive, microaerophilic or anaerobic bacterium which ferments sugars with the production of acids including lactic acid as the predominantly produced acid, acetic acid and propionic acid. The industrially most useful lactic acid bacteria are found among *Lactococcus* spp., *Streptococcus* spp., *Lactobaccillus* spp., *Leuconostoc* spp., *pediococcus* spp., *Brevibacterium* spp. And *Propionibacterium* spp. Additionally, lactic acid producing bacteria belonging to the group of the strict anaerobic bacteria, bifidobacteria, i.e. *Bifidobacterium* spp., which are frequently used as food starter cultures alone or in combination with lactic acid bacteria, are generally included in the group of lactic acid bacteria. A presently preferred host cell species is *Lactococcus lactis*.

Following the transformation of the selected lactic acid bacterial host species, the transformed bacterium is cultivated under conditions where the fusion protein is expressed. The culture medium used to cultivate recombinant lactic acid bacterial host cells can be any conventional medium which is suitable for the purpose e.g. with respect to its nutrient composition and pH. In useful embodiments, the host cells are cultivated under anaerobic conditions in an industrial production scale. In the present context, large scale production or industrial production scale indicates that the volume of culture medium in the fermentation vessel is at least 1 liter, such as at least 5 liter e.g. at least 10 liter. It is also envisaged that the volume can be larger such as at least 100 liter including at least 250 liter.

The choice of specific fermentation conditions such as fermentation time and temperature depends on the requirements of the selected lactic acid bacterial host cell. Generally, the fermentation time is in the range of 10 to 30 hours such as in the range of 20-30 hours.

Preferably, the amount of fusion protein that is secreted into the culture medium after completion of the lactic acid bacterial fermentation process is at least 20 mg/l, such as at least 50 mg/l, preferably at least 100 mg/l e.g. at least 250

mg/l including at least 500 mg/l. The monomeric form of the cysteine rich protein fused to a glutamate rich protein can be enhanced by modifying the redox potential of the medium in which the protein is secreted into. This is achieved by the addition of reduced forms of L-cysteine or DTT or glutathione or TCEP or cysteamine or any other small sulfhydryl containing compound capable of reducing cystines in proteins in the range of 1-20 mM, preferably 10 mM of L-cysteine to the culture medium.

In a final step of the method according to the invention, the fusion protein is purified. Depending on whether or not the coding sequence is associated with a signal sequence which affects the secretion of the fusion protein across the cell membrane and into the culture medium, the step of purification includes either the isolation of the fusion protein from the host cell (no signal sequence) or that it is isolated directly from the culture medium. These steps can be carried out using any conventional method of down-stream processing.

Generally, it is preferred that the fusion protein is secreted into the culture medium rather than being accumulated intracellularly, as it appears that a polypeptide that is not subjected to extraction from the host cell may have a higher bioreactivity than a cell-extracted derived polypeptide.

Thus, when the fusion protein is secreted into the culture medium, the first step of purification is a separation of the host cell e.g. by centrifugation or filtration followed by isolating the fusion protein from the supernatant or the filtrate. It is preferred that the fusion protein amounts to at least 25% of the total protein content of the supernatant or the filtrate such as at least 30%, including at least 40% e.g. at least 50%.

Generally, the supernatant or filtrate is subjected to a step of concentration and/or at least partial purification using any conventional method for such purposes such as e.g. cross-flow filtration, salting out, immobilized metal-ion affinity chromatography, immunoaffinity chromatography, hydrophobic interaction chromatography and/or ion exchange chromatography. In preferred embodiments, the concentration and at least partially purified preparation of the fusion protein contains at least 0.5 mg/ml of fusion protein, such as at least 1.0 mg/ml including at least 1.5 mg/ml e.g. at least 2.0 mg/ml.

The amount of correctly folded monomeric form of the cysteine rich protein fused to a glutamate rich protein can be enhanced in the initial partial purification by treatment of the material with a buffer containing a controlled buffer redox potential.

The crude or optionally partially purified fusion protein preparation obtained by the purification steps as defined above may be used as such or it may be formulated e.g. splitting the fusion protein in its components, to provide a storage stable and convenient composition such as an immunogenic composition or a vaccine. Thus, such ready-to-use composition may e.g. include preserving agents, polypeptide stabilizing agents or substances which enhances the reactivity of the fusion protein. Additionally, a crude protein preparation may be subjected to further concentration or dilution in order to obtain a pre-determined amount or activity of the ready-to-use composition such as an immunogenic composition or a vaccine.

Vaccine, Protein

The invention pertains to an immunogenic composition, a vaccine comprising a fusion protein according to the invention and the production hereof. In order to ensure optimum performance of such a vaccine composition it is preferred that it comprises an immunologically and pharmaceutically acceptable carrier, vehicle or adjuvant.

An effective immunogenic composition or vaccine, wherein a protein of the invention is recognized by the animal, will in an animal model be able to decrease parasite load in blood and target organs, prolong survival times and/or diminish weight loss after challenge with a malarial parasite, compared to non-vaccinated animals.

Furthermore, the fusion protein of the invention may be coupled to a carbohydrate or a lipid moiety, e.g. a carrier, or a modified in other ways, e.g. being acetylated.

When produced in a microorganism the fusion protein of the invention will normally not be acetylated if no special measures are taken. The acetylation may be advantageous as acetylated polypeptides may be more stable in cell, blood or body and tissue fluids. Furthermore, the acetylation may confer the polypeptide with a structure and confirmation which mimics the structure and confirmation of the native *P. falciparum* antigen.

Suitable carriers are selected from the group consisting of a polymer to which the polypeptide(s) is/are bound by hydrophobic non-covalent interaction, such as a plastic, e.g. polystyrene, or a polymer to which the polypeptide(s) is/are covalently bound, such as a polysaccharide, or a polypeptide, e.g. bovine serum albumin, ovalbumin or keyhole limpet haemocyanin. Suitable vehicles are selected from the group consisting of a diluent and a suspending agent. The adjuvant is preferably selected from the group consisting of dimethyldi-octadecylammonium bromide (DDA), Quil A, poly I:C, aluminium hydroxide, Freund's incomplete adjuvant, IFN-γ, IL-2, IL-12, monophosphoryl lipid A (MPL), Treholose Dimycolate (TDM), Trehalose Dibehenate and muramyl dipeptide (MDP).

Preparation of vaccines which contain peptide sequences as active ingredients is generally well understood in the art, as exemplified by U.S. Pat. Nos. 4,608,251; 4,601,903; 4,599,231 and 4,599,230, all incorporated herein by reference.

Other methods of achieving adjuvant effect for the vaccine include use of agents such as aluminum hydroxide or phosphate (alum), synthetic polymers of sugars (Carbopol), aggregation of the protein in the vaccine by heat treatment, aggregation by reactivating with pepsin treated (Fab) antibodies to albumin, mixture with bacterial cells such as *C. parvum* or endotoxins or lipopolysaccharide components of gram-negative bacteria, emulsion in physiologically acceptable oil vehicles such as mannide mono-oleate (Aracel A) or emulsion with 20 percent solution of a perfluorocarbon (Fluosol-DA) used as a block substitute may also be employed. Other possibilities involve the use of immune modulating substances such as cytokines or synthetic IFN-γ inducers such as poly I:C in combination with the above-mentioned adjuvants.

Another interesting possibility for achieving adjuvant effect is to employ the technique described in Gosselin et al., 1992 (7). In brief, a relevant antigen such as an antigen of the present invention can be conjugated to an antibody (or antigen binding antibody fragment) against the Fcγ receptors on monocytes/macrophages.

The vaccines are administered in a manner compatible with the dosage formulation, and in such amount as will be therapeutically effective and immunogenic. The quantity to be administered depends on the subject to be treated, including, e.g., the capacity of the individual's immune system to mount an immune response, and the degree of protection desired. Suitable dosage ranges are of the order of several hundred micrograms active ingredient per vaccination with a preferred range from about 0.1 μg to 1000 μg, such as in the range from about 1 μg to 300 μg, and especially in the range from about 10 μg to 50 μg. Suitable regimens for initial administration

and booster shots are also variable but are typified by an initial administration followed by subsequent inoculations or other administrations.

The manner of application may be varied widely. Any of the conventional methods for administration of a vaccine are applicable. These are believed to include oral application on a solid physiologically acceptable base or in a physiologically acceptable dispersion, parenterally, by injection or the like. The dosage of the vaccine will depend on the route of administration and will vary according to the age of the person to be vaccinated and, to a lesser degree, the size of the person to be vaccinated.

The vaccines are conventionally administered parenterally, by injection, for example, either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, in some cases, oral formulations. For suppositories, traditional binders and carriers may include, for example, polyalkalene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1-2%. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and advantageously contain 10-95% of active ingredient, preferably 25-70%.

In many instances, it will be necessary to have multiple administrations of the vaccine. Especially, vaccines can be administered to prevent an infection with malaria and/or to treat established malarial infection. When administered to prevent an infection, the vaccine is given prophylactically, before definitive clinical signs or symptoms of an infection are present.

Due to genetic variation, different individuals may react with immune responses of varying strength to the same protein. Therefore, the vaccine according to the invention may comprise several different proteins in order to increase the immune response. The vaccine may comprise two or more polypeptides or immunogenic portions, where all of the proteins are as defined above, or some but not all of the peptides may be derived from *P. falciparum* or other microorganisms. In the latter example, the polypeptides not necessarily fulfilling the criteria set forth above for polypeptides may either act due to their own immunogenicity or merely act as adjuvants.

The vaccine may comprise 1-20, such as 2-20 or even 3-20 different proteins or fusion proteins, such as 3-10 different proteins or fusion proteins.

The invention also pertains to a method for immunising an animal, including a human being, against malaria caused by e.g. *P. falciparum*, comprising administering to the animal the fusion protein of the invention, or a vaccine composition of the invention as described above, or a living vaccine described below.

The invention also pertains to a method for producing an immunologic composition according to the invention, the method comprising preparing, synthesising or isolating a fusion protein according to the invention, and solubilizing or dispersing the fusion protein in a medium for a vaccine, and optionally adding other antigens and/or a carrier, vehicle and/or adjuvant substance.

Another aspect of the invention is producing the hybrid protein of the invention in a recombinant microorganism which, besides expressing the DNA sequence encoding the present hybrid protein, additionally expresses one or more antigens having a therapeutic or protective effect against another disease than malaria, e.g. tuberculosis. These other antigens can be expressed as separate antigens or as fused to the hybrid protein of the present invention. Examples of other antigens effective against *M. tuberculosis* are ESAT6, CFP7, CFP10, CFP29, ORF2c, TB 13, MPT59, α-crystalline, Rv0285 and hybrids hereof, but the concept is not limited to tuberculosis or antigens against tuberculosis alone.

Vaccine DNA.

The nucleic acid fragments of the invention may be used for effecting in vivo expression of antigens, i.e. the nucleic acid fragments may be used in so-called DNA vaccines as reviewed in Ulmer et al 1993, which is included by reference.

Hence, the invention also relates to a vaccine comprising a nucleic acid fragment according to the invention, the vaccine effecting in vivo expression of antigen by an animal, including a human being, to whom the vaccine has been administered, the amount of expressed antigen being effective to confer substantially increased resistance to infections caused by *P. falciparum* in an animal, including a human being.

The efficacy of such a DNA vaccine can possibly be enhanced by administering the gene encoding the expression product together with a DNA fragment encoding a polypeptide which has the capability of modulating an immune response.

Live Recombinant Vaccines

One possibility for effectively activating a cellular immune response for a vaccine can be achieved by expressing the relevant antigen in a vaccine in a non-pathogenic microorganism or virus. Well-known examples of such microorganisms are *Mycobacterium bovis* BCG, *Salmonella* and *Pseudomona* and examples of viruses are Vaccinia Virus and Adenovirus.

Therefore, another important aspect of the present invention is an additional quality of the living BCG vaccine presently available, wherein one or more copies of a DNA sequence encoding one or more fusion proteins as defined above has been incorporated into the genome of the microorganism in a manner allowing the micro-organism to express and secrete the protein. The incorporation of more than one copy of a nucleotide sequence of the invention is contemplated to enhance the immune response.

Another aspect of the invention is a non-pathogenic microorganism, such as e.g. *Lactococcus lactis* or BCG, expressing the DNA sequence encoding one or more fusion proteins as defined above and additionally expressing one or more antigens having a therapeutic or protective effect against a disease different from malaria, such as e.g. tuberculosis caused by *Mycobacterium tuberculosis*. These other antigens can be expressed as separate antigens or as fused to the hybrid protein of the present invention. Examples of other antigens effective against *M. tuberculosis* (identified by their Sanger database accession number) are Rv3875 (ESAT6), Rv1886c (Ag85B), Rv0288 (CFP7), Rv3874 (CFP10), Rv0798c (CFP29), Rv2031c (α-crystalline) and Rv0285 or fragments or hybrids hereof most preferable the ESAT6-Ag85B hybrid, but the concept is not limited to tuberculosis or antigens against tuberculosis alone.

The effect of such a DNA-vaccine can possibly be enhanced by administering the gene encoding the expression product together with a DNA fragment encoding a polypeptide which has the capability of modulating an immune response. For instance, a gene encoding lymphokine precursors or lymphokines (e.g. INF-γ, IL-2, IL-12) could be administered together with the gene encoding the immunogenic fusion protein, either by administering two separate DNA fragments or by administering both DNA fragments included in the same vector.

Another possibility is to integrate the DNA encoding the polypeptide according to the invention in an attenuated virus such as the vaccinia virus or Adenovirus (40). The recombinant vaccinia virus is able to replicate within the cytoplasma of the infected host cell and the protein of interest can therefore induce an immune response, which is envisioned to induce protection against malaria.

Therapeutic Vaccine

The invention also relates to the use of a fusion protein or nucleic acid of the invention for use as therapeutic vaccines as have been described in the literature exemplified by D. Lowry (15). Antigens with therapeutic properties may be identified based on their ability to diminish the severity of malarial infection in experimental animals or prevent reactivation of previous infection, when administered as a vaccine. The composition used for therapeutic vaccines can be prepared as described above for vaccines.

Transmission-blocking Vaccines

The objective of a transmission-blocking vaccine is to prevent an individual from becoming infected with *Plasmodium* parasites by mosquito bites of the *Anopheles* vector. As a result, the spread of malaria in the population is expected to decrease with subsequent reduction of the disease. Transmission-blocking vaccines are based on sexual- or sporogonic-specific antigens and designed to elicit transmission-blocking antibodies with the ultimate aim to arrest the development of sporogonic stages inside the mosquito. Human transmission-blocking antibodies are passively ingested together with parasites when mosquitoes take a blood meal and will bind to the parasites thereby interfering with zygote formation.

LEGENDS TO FIGURES

FIG. **1**: Structures and properties of specific subdomains cloned. The top line shows the native Pfs45/48 with the position of the 16 cysteine residues indicated. Lines below show the portion of Pf48/45 included in the 16C, 10C, 6C, 6N, and 10N constructs.

FIG. **2**: Schematic representation the pLEA 5 expression constructs used in *L. lactis*. The position of vector-encoded promoter P170, Shine-Dalgarno sequence (SD), and 310mut2 signal peptide are indicated. The signal peptidase is predicted to cleave between amino acid nos. 32 and 33, thus leaving Ala-Glu residues in the N-terminal end of the mature recombinant proteins. The nucleotide numbering of glurp and Pfs48/45 was relative to A in the ATG codon of M59706 and (XM_001350145), respectively.

FIG. **3**: Coomassie stained SDS-PAGE of culture supernatant. Lane 1: 5 μl HiMark Protein Ladder, Lane 2-4: culture supernatant taken after 16 h, 18 h and 20 h of cultivation respectively. Loaded 20 μl sample +4 μl 6×SDS sample loading buffer pr. well. Lane 5-7: 1 μg, 0.5 μg and 0.2 μg of Bovine Serum Albumin respectively. Estimated yield of recombinant protein after 20 h of cultivation is 25-50 mg/L (20 μl on an SDS-PAGE/Coomassie gel gives intensity between 0.5 and 1.0 μg BSA).

FIG. **4**: Separation of different forms of R0-10C-6H on a 16/60 Superdex 200 column. The X-axis is the retention volume (in ml) and the black chromatogram shows the UV280 signal (seen on the Y-axis in arbitrary units). The fraction indicators on the X-axis indicate the fractionation profile. Fraction A4-A7 (approx. retention volume between 45-53 ml) corresponds to peak 1 and contains mainly multimeric R0-10C-6H. Fractions A8-A9 (approx. retention volume between 53 and 57 ml) contains a mixture of dimeric and monomeric forms of R0-10C-6H. Fraction A10-B12 (approx. retention volume between 57 and 65 ml) contains the monomeric form of R0-10C-6H.

FIG. **5**: Coomassie stained SDS-PAGE of fraction pools from the gel filtration of R0-10C-6H seen in FIG. **4**. 3 μg of protein is loaded in each well. Samples are loaded with and without the presence of 50 mM DTT.

FIG. **6**: 1-SITE ELISA of purified R0-10C-6H with (PBS-ACRB) or without (PBS-ACBB) redox buffer wash. Protein was coated with two fold dilution of protein starting at 1000 ng. Anti-hexahistidine(C-term)-HRP was used as detecting antibody and TMB for developing.

FIG. **7**: 2-SITE ELISA of purified R0-10C-6H with (PBS-ACRB) or without (PBS-ACBE) redox buffer wash. 250 ng of monoclonal antibody, 85RF45.1, was coated as capturing antibody and incubation with two fold dilution of protein starting at 1000 ng. Anti-hexahistidine(C-term)-HRP was used as detecting antibody and TMB for developing.

FIG. **8**: Immunization schedule. Rats where divided into two groups (Group 1 and Group 2) with three rats in each. Group 1 was injected with the PBS-ACRB protein and Group 2 with the PBS-ACBB protein. At day zero (2-3 weeks prior to priming immunization) a pre-bleed was taken. Three boosts where made with 3 weeks apart starting three weeks after the priming Bleeds where taken 1 week after each of the boosts with 3rd bleed being the final bleed.

FIG. **9**: Comparison in gametocyte ELISA reactivity. Sera were tested for reactivity towards native Pfs48/45 from gametocyte extract. Gametocyte extract was coated on the plate. The rat sera was used in two-fold dilutions (starting from 100 fold diluted) as primary antibody and HRP labeled rabbit anti-rat as secondary antibody was used as detecting antibody with TMB for developing. The points represent the mean and standard deviation of the 3rd bleed from the three animals in each group.

FIG. **10**: Comparison between individual animals from Group 1. The same data as for FIG. **9**, but with each point representing each animal.

FIG. **11**: SDS-PAGE of samples from immunopurification. Loaded 5 μg of protein in each well +/DTT and used Coomassie staining.

FIG. **12**: Western blot of samples from immunopurification. Loaded 0.5 μg of protein in each well +/−DTT and transferred to membrane. Used 85RF45.1 as primary and HRP labeled rabbit anti-rat as secondary antibody. Used chemiluminescence for detection.

FIG. **13**: 1-SITE ELISA of immunopurified R0-10C-6H. Protein was coated with two fold dilution of protein starting at 1000 ng. Anti-hexahistidine(C-term)-HRP was used as detecting antibody and TMB for developing.

FIG. **14**: 2-SITE ELISA of immunopurified R0-10C-6H. 250 ng of monoclonal antibody, 85RF45.1, was coated as capturing antibody and incubation with two fold dilution of protein starting at 1000 ng. Anti-hexahistidine(C-term)-HRP was used as detecting antibody and TMB for developing.

FIG. **15**. Expression of Pfs45/48 fragments in pAMJ328: (A) SDS-PAGE of culture supernatants; (A-F) lane 1 MG1363 transformed with pAMJ328 (control), lanes 2-5 MG1363 transformed with pCNR5 (Pfs45/48_16C), pCNR6 (Pfs45/48_10C), pCNR7 (Pfs45/48_6N), and pCNR8 (Pfs45/48_10N), respectively. (B; C) Western blots of culture supernatants. (B) A polyclonal rabbit antibody against Pfs45/48 was used as primary antibody and a swine anti-rabbit antibody was used as secondary antibody. (C) A rat monoclonal antibody raised against the Pfs45/48 epitope V was used as primary antibodies and goat anti-rat IgG were used as secondary antibody. (D) SDS-PAGE of intracellular and cell-

associated proteins. (E; F) Western blots of intracellular and cell-associated proteins. (E) Antibodies are as described in (B). (F) Antibodies are as described in (C).

FIG. **16**. Expression of Pfs45/48 fragments in pAMJ219: (A) SDS-PAGE of culture supernatants; (A-F) lane 1 MG1363 transformed with pAMJ219 (control), lanes 2-5 MG1363 transformed with pCNR9 (Pfs45/48_16C), pCNR10 (Pfs45/48_10C), pCNR11 (Pfs45/48_6N), and pCNR12 (Pfs45/48_10N), respectively. (B; C) Western blots of culture supernatants. (B) A polyclonal rabbit antibody against Pfs45/48 was used as primary antibody and a swine anti-rabbit antibody was used as secondary antibody. (C) A rat monoclonal antibody raised against the Pfs45/48 epitope V was used as primary antibody and goat anti-rat IgG was used as secondary antibody. (D) SDS-PAGE of intracellular and cell-associated proteins. (E; F) Western blots of intracellular and cell-associated proteins. (E) Antibodies are as described in (B). (F) Antibodies are as described in (C).

FIG. **17**. Schematic representation of pPSM1013, pAMJ328 and, pAMJ219 and the expression constructs used in *L. lactis*. The position of vector-encoded restriction sites mentioned in the text, promoter P170, Shine-Dalgarno sequence (SD), 310mut2—and, USP-45 signal peptide are indicated. The nucleotide numbering of Pfs45/48 is relative to A in the ATG codon.

FIG. **18**: Purification of RO-MSP3-6C-6H on (A) Step 1: a Hitrap crude FF Ni^{++}-column, (B) Step 2: size exclusion chromatography on a Superdex 200S column and (C) Step 3: ion exchange chromatography on a Q HP column.

EXAMPLES

Example 1

Expression of the R0-10C-6H in *L. lactis*

Construction of Plasmids

The 1.4 kb GLURP-R0 fragment (bp 79-1500) was amplified from gDNA from the *P. falciparum* line F32 using forward primer GA52 (ccagatctacaagtgagaatagaaataaacgaatc) and reverse primer GA4 (ctatacttgatataacctttttcagtattatctgcttcatgctcgctttttttccgattc).

The 0.8 kb 10C fragment of Pfs48/45 (bp 475-1282) was amplified from gDNA from the *P. falciparum* line 3D7 using forward primer GA12 (gaatcggaaaaaagcgagcatgaagcagataatactgaaaaggttatatcaagtatag) and reverse primer GA53 (ccagatctctaatggtgatgatggtgatgtgctgaatctatagtaactgtcatataag).

These two amplicons were fused inframe by amplifying 28 ng of the R0 fragment with 16 ng of the 10C fragment using primers GA52 and GA53. The fusion was then treated with amplicon polymerase for 15 minutes at 72° C. This topo treated fragment was ligated into the Topo vector pCR2.1 (Invitrogen) and the sequence was verified. The Topo product was digested with BglII and the resulting fragment cloned into a BglII digested pKBR11 vector yielding pLEA_5 (FIG. **2**).

Protein Description

The recombinant protein (after processing of the SP_{310} signal peptide) is composed of four vector encoded residues (AERS) followed by GLURP-$R0_{27-500}$, Pfs48/45-$10C_{159-428}$ and finally a six histidine C-terminus (R0-10C-6H). The theoretical molecular weight of the protein is 89.8 kDa of which 30.7 kDa originates from the 10C fragment. The pI and the extinction coefficient are calculated to be 4.9 and 2.7 (at 1%), respectively.

Production of Recombinant R0-10C-6H Protein

Working Cell Bank

pLEA_5 was transformed into the *L. lactis* strain MG1363 and plated on YPDKN[E] selective plate. A colony was picked into 50 ml YPDKN[E] selective medium in a 50 ml tube. Culture was incubated overnight at 30° C. at 150 RPM. Following the overnight inoculation, 350 µl of the pre-culture is used to inoculate a 35 ml YPDKN[E] selective medium in a 50 ml tube. The culture is harvested (3.700 g, 15 min, 4° C.) at OD_{600}=1-3. Cells were washed in 20 ml cold YPDKN non-selective medium and spun down (3.700 g, 15 min, 4° C.). Finally, cells were resuspended in 10 ml non-selective cryopreservation solution YPDKNG (final cell density OD_{600}=12.5), and 200 µl is dispensed into 2 ml cryotubes (27 tubes), and stored in a box at −80° C.

Fermentation

Day 1

A Working Cell Bank vial was thawn and inoculated into 50 ml prewarmed YPD[3%] in a 50 ml tube. Pre-culture was grown @ 30° C. with gentle shaking (150 RPM).

Inoculation of fermentor containing 1 liter Basic LAB Medium[1] was done with syringe and needle through septum on the fermentor head-piece, when OD_{600nm}>0.6 (approx. 4-5 hours).

[1]1% yeast extract, 2% Soya peptone, 3% dextrose, 0.1% potassium phosphate dibasic, 0.17% ammonium sulphate dibasic, 0.12% ammonium phosphate dibasic, 0.26% sodium citrate tribasic dihydrate, 0.025% magnesium sulphate heptahydrate, 0.0034% manganese sulphate monohydrate.

Fermentation @ 30° C.; 150 RPM; pH=6.5 (adjusted with 2 M sodium hydroxide), no DO electrode; no aeration; no feed

Culture grows to OD_{600nm} Induction of protein expression when culture reaches low pH.

Grown overnight.

Day 2

Cells were removed (10.000 g, 4° C., 10 min).

Estimated yield of recombinant protein is 25-50 mg/L (20 µl on an SDS-PAGE/Coomassie gel gives intensity between 0.5 and 1.0 µg BSA, (FIG. **3**)).

Purification

Concentration and Diafiltration

Supernatant was concentrated to approx. 200 ml on a Quixstand system mounted with a 30.000 MWCO Hollow-Fiber Cartridge (GE Healthcare). Then the sample was diafiltrated against 1 liter 50 mM sodium phosphate (pH 7.0) (PBS-DFB1) and 1 liter 50 mM sodium phosphate (pH 7.0), 250 mM sodium chloride (PBS-DFB2), before being concentrated to approx. 125 ml. Sample was filtered (0.2 µm filter) and stored at 4° C. untill purification. Concentration and diafiltration was done at room temperature (20-22° C.). These procedures do not result in a major loss of recombinant protein.

Affinity Purification

Processed supernatant was mixed with 50 mM sodium phosphate (pH 7.0), 250 mM sodium chloride, 200 mM imidazole (PBS-ACEB) 9 to 1, to reach 20 mM imidazole in the sample. Purification of 6×his-tagged proteins was done on a ÄKTAxpress mounted with a 5 ml HistTrap HP (GE Healthcare). Briefly, column was equilibrated with 50 mM sodium phosphate (pH 7.0), 250 mM sodium chloride, 20 mM imidazole (PBS-ACBB), before loading sample. Unbound sample was washed out with PBS-ACBB. The column was then washed with 50 mM sodium phosphate (pH 7.0), 250 mM sodium chloride, 20 mM imidazole, 4/0.4 mM reduced glutathione/oxidized glutathione (PBS-ACRB) at 1 ml/min for 30 minutes, before a step elution with PBS-ACEB was done. All steps where run at 8° C. with a flow of 4 ml/min

unless noted otherwise. Total yield of R0-10C-6H at this stage is up to 35 mg pr. liter culture.

Gel Filtration

The affinity purified protein is loaded on a 16/60 HiLoad S-200 column to separate the monomeric form of R0-10C-6H from the multimeric forms. It was run with 50 mM 50 mM Tris-HCl (pH 8.0), 100 mM sodium chloride (TBS-GFB). Approximately 40% was in the monomeric form (judged from the chromatogram (FIG. **4**)), which gives a monomer yield in the affinity chromatography step of 6-14 mg pr. liter culture. However, due to the loss in the purification system (approx. 70% recovery) and because baseline separation was not achieved (approx. 60% is separated. Eg. fractions A10-B12 are monomeric (FIG. **5**)), the actual recovery of the >95% pure monomeric R0-10C-6H after the gel filtration was approx. 6 mg pr. liter culture.

Ion-exchange Chromatography

Fractions containing the monomeric form of R0-10C-6H are pooled and purified on a 1 ml Q HP column (GE Healthcare). Briefly, column is equilibrated with 50 mM Tris-HCl (pH 8.0), 100 mM sodium chloride (TBS-IECB), before loading sample. Unbound sample was washed out with TBS-IECBB before a step elution with 50% 50 mM Tris-HCl (pH 8.0), 1 M sodium chloride (TBS-IECEB) is done. Final yield of >95% pure monomeric R0-10C-6H was approx. 5 mg pr. liter culture.

TABLE 3

Protein purification overview

Step	Purity R0-10C-6H	Purity mono-mer	Amounts R0-10C-6H	Amounts monomer	Recovery (loss*)
Fermentation	60%	24%	25-50 mg	10-20 mg	40% (60%)
Diafiltration	60%	24%	25-50 mg	10-20 mg	40% (0%)
Affinity	>95%	40%	15-35 mg	6-14 mg	28% (30%)
Gel filtration	>95%	>95%	3-6 mg	3-6 mg	12% (60%)
Ion-exchange	>95%	>95%	2.5-5 mg	2.5-5 mg	10% (20%)

*Loss is the estimated percentage of protein loss in given step. E.g. in the Fermentation step loss is the amount of the total R0-10C-6H which is in the multerimeric forms (judged from FIG. 5).

Example 2

Immunogenicity of Recombinant R0-10C-6H

The effect of PBS-ACRB washing step was tested by purifying R0-10C-6H with and without the PBS-ACRB washing step (without was done by exchanging PBS-ACRB with PBS-ACBB). The protein was tested in a 1-SITE and a 2-site ELISA to determine the potency of each sample. In the 1-SITE ELISA different concentrations of antigen was coated and detected with commercial HRP conjugated anti-hexahistidine antibody (FIG. **6**). In the 2-SITE ELISA first the monoclonal antibody (85RF45.1) against Pfs48/45 was coated as capturing antibody on an ELISA plate, followed by blocking with skimmed milk. Different concentrations of antigen were applied and finally bound antigen was detected using commercial HRP conjugated anti-hexahistidine antibody (FIG. **7**). The reactivity was more than two times higher with the PBS-ACRB wash compared to without (Table 4).

TABLE 4

	EC50 (1-SITE)	EC50 (2-SITE)	POTENCY	REL. POTENCY (PBS-ACBB)
PBS-ACRB	130.1	17.2	7.6	2.18
PBS-ACBB	139	40.1	3.5	1.00

Two groups of three rats each were immunized with different R0-10C-6H purifications adjuvanted with Freund's adjuvant. The groups were immunized 4 times according to immunization schedule (FIG. **8**) with either 12.5 μg R0-10C-6H purified with the PBS-ACRB wash (Group 1), 25 μg R0-10C-6H purified without the PBS-ACRB wash (Group 2). The sera from the bleed after the last immunization (3^{rd} bleed) were tested in a gametocyte ELISA (17). The level of reactivity towards gametocyte extract in Group 1 is higher compared to Group 2, with EC50 values of 417 and 54 fold serum dilution, respectively (FIG. **9**). When comparing the individual sera from Group 1, some difference can be seen (FIG. **10**).

Example 3

Immunopurification of Correctly Folded R0-10C-6H

To immunopurify correctly folded R0-10C-6H 1.8 mg of 85RF45.1 was coupled to a 1 ml NHS-activated HiTrap column (GE-HEalthcare, 17-0716-01), then IMAC purified R0-10C-6H from 200 ml supernatant (approx. 15 mg) was run through the column and bound protein was eluted according to manufacturers description. Fractions containing the desired protein were concentrated to 300 μl using a Vivaspin column. The input (IN), runthrough (RT) and pooled concentrated eluate (E1-3) were analysed by SDS-PAGE, Western blotting, and by 1-SITE and a 2-SITE ELISA (FIG. **11-14**, respectively). The SDS-PAGE shows that the majority of the eluted protein is monomeric, but some smaller products have been co-purified. On the Western blot a very faint band can be seen in the input, while a clear band is visible in the E1-3 fractions. The relative potency of the correctly folded monomer compared to the input can be calculated from the relative EC50 value ($EC50_{E1\text{-}3}/EC50_{IN}$) in the 2-SITE ELISA divided by the same value in the 1-SITE ELISA (Table 6). The relative potency of the eluted sample is 13.07 and of the runthrough is 0.04, thus together with the Western blot it is evident that only correctly folded monomeric R0-10C-6H (E1-3) has been separated from the non-correctly folded monomeric and multimeric R0-10C-6H (RT). Calculating backwards using E1-3 as reference sample the input has a relative potency of 0.08 which equals 8% correctly folded R0-10C-6H.

TABLE 6

	EC50 (1-SITE)	EC50 (2-SITE)	POTENCY	REL. POTENCY (IN)	REL. POTENCY (E1-3)
IN	118.5	49.1	2.4	1.00	0.08
RT	65.6	619.6	0.1	0.04	0.00
E1-3	30.1	1.0	31.5	13.07	1.00

Example 4

Expression of Individual Pfs48/45 Fragments

These experiments aimed to produce four overlapping Pfs48/45 fragments, 16C, 10C, 6N, and 10N as individual recombinant proteins in *Lactococcus lactis* (FIG. **1**).

Expression of Pfs45/48 16C, 10C, 6N, and 10N in pAMJ328

Four different fragments of the Pfs45/48 gene were cloned inframe with the signal sequence SP310mut2 into the plasmid pAMJ328. The resultant plasmids, pCNR5 (Pfs45/48_16C), pCNR6 (Pfs45/48_10C), pCNR7 (Pfs45/48_6N), and pCNR8 (Pfs45/48_10N), were transformed into the *L. lactis* strain MG1363. MG1363 cells carrying the expression plasmids pCNR5, pCNR6, pCNR7, and pCNR8 were grown in *L. lactis* media containing 1% (w/v) glucose and 10 μg/ml of erythromycin. The growth of the cultures was monitored by measuring OD_{600} every ½-1 h. Start OD_{600}'s were 0.04 and pH values were approximately 7.5. After 5½ h of growth, pH decreased to approximately 6.0 and 1 h later cells had entered the stationary growth phase (OD_{600}=~1.75). The expression and localization of rPfs45/48 constructs was analyzed by SDS-PAGE and Western blot of cultures harvested two hours after cells had entered the stationary growth phase. A polyclonal antiserum and a monoclonal antibody (85RF45.5) were used for rPfs45/48 detection. Proteins from 5 ml of each culture supernatant were separated on a 4-12% SDS-gel and stained with Coomassie brilliant blue (FIG. **15**A). SDS-PAGE analysis of Pfs45/48 culture supernatants did not reveal the presence of any additional or more apparent protein bands when lanes were compared to the control in which MG1363 cells had been transformed with pAMJ328. Western blot analysis did, however, reveal expression and secretion of two of the prepared Pfs45/48 constructs: rPfs45/48_6N and rPfs45/48_10N (FIG. **15**C; lanes 4-5). The molecular weight of the bands matches the theoretical weight of Pfs45/48_6N (17 kDa) and Pfs45/48_10N (32 kDa). Pfs45/48_6N and Pfs45/48_10N could only be detected with the monoclonal anti-Pfs45/48 epV antibody as no bands were revealed on the Western blot in which the polyclonal antiserum was used for detection (FIG. **15**B). As the anti-Pfs45/48 epV antibody can not be used for detecting the 10C construct of Pfs45/48 it remains uncertain if expression and secretion also has been obtained for this construct. The level of Pfs45/48_6N and Pfs45/48_10N expressed and secreted is, however, estimated to be low. One possibility is that the rPfs45/48 fragments remain poorly, and/or are not at all secreted, when fused to the signal peptide SPmut2. This would lead to intracellular accumulation. Western blot analysis of intracellular and cell associated proteins did seem to show the presence of Pfs45/48_16C (46 kDa), Pfs45/48_10C (31 kDa), and Pfs45/48_10N (32 kDa) (FIG. **15**D; lanes 2, 3, and 5). The faint protein bands matching these three Pfs45/48 constructs were only detected on the Western blot incubated with the polyclonal antiserum. From these analyses it seems as the general expression level of the four Pfs45/48 constructs prepared in pAMJ328 and expressed in *L. lactis* MG1363 is low.

Expression of Pfs45/48 16C, 10C, 6N, and 10N in pAMJ219

To investigate whether pAMJ219 could be a better expression vector for the production and secretion of Pfs45/48 constructs all four Pfs45/48 fragments were cloned into the Usp45 containing pAMJ219. The growth of *L. lactis* MG1363 transformed with pCNR9 (Pfs45/48_16C), pCNR10 (Pfs45/48_10C), pCNR11 (Pfs45/48_6N), and pCNR12 (Pfs45/48_10N) was similar to that of the control plasmid. However, we were unable to detect any of the rPfs45/48 fragments by SDS-PAGE or by Immuno blot analysis of secreted as well as cellular proteins were (FIG. **16**).

Conclusion

Two different expression vectors (pAMJ328 and pAMJ219) were used for the production of four different but overlapping Pfs45/48 fragments in *L. lactis* MG1363. Expression of the Pfs45/48 constructs was only seen in pAMJ328 in which the constructs had been cloned inframe with the signal peptide SPmut2. No expression was detected when the constructs were cloned into pAMJ219. In general expression levels are low and only minor amounts of rPfs45/48_6N and rPfs45/48_10N are detectable in the culture medium. Pfs45/48_16C, Pfs45/48_10C and some of the rPfs45/48_10N seems to remain inside the cells.

Example 5

Materials and Methods

Bacterial Strains and Plasmids

E. coli Xl-1 blue (Stratagene), used as primary host for the construction and propagation of plasmids, was grown at 37° C. in Luria-Bertani (LB) broth supplemented with erythromycin (100 μg/ml). *L. Lactis* MG1363 (6) was grown at 30° C. in *L. lactis* media (1% (w/v) soya peptone, 1% (w/v) yeast extract, 0.1% (w/v) $MgSO_4 \times 7H_2O$, 0.1% (w/v) ascorbin acid, 3.8% (w/v) glycerophosphate) containing 1% (w/v) glucose and 10 μg/ml of erythromycin. Solidified LB and M17 media was supplemented with 250 and 5 μg/ml of erythromycin, respectively. The vector, pPSM1013 (FIG. **17**), is a high-copy number expression plasmid based on the pAMβ1 replicon (26) containing multiple cloning sites allowing the construction of in-frame fusions with the modified and highly efficient secretion signal peptide SP310mut2 (20). The vector, pAMJ328 (FIG. **17**) is derived from pPSM1013 by deleting all lacZ regulatory sequences to avoid transcription from the lac promoter and by creating a new cloning region devoid of the signal peptide (10). The vector, pAMJ219 (FIG. **17**) is a low-copy number expression plasmid containing the minimal replicon pCIT (19). The multiple cloning site comprising BglII, PstI and SalI restrictionsites is located between by position 3572 and position 3589 allowing the construction of in-frame fusions with the signal peptide of Usp45 (the main secreted protein in *L. lactis*) efficiently recognized by the lactococcal secretion machinery. All vectors used in the study contain derivatives of the same promoter, P170, which is upregulated at low pH during the transition to stationary phase.

Construction of Plasmids Expressing Pfs48/45 16C, 10C, 6N and 10N in *L. lactis*

All plasmids were constructed in *E. coli* Xl-1-blue and transformed into *L. lactis*

MG1363 by electroporation as described (8). All plasmid constructions were verified by DNA sequencing. The key plasmids constructed in Example 4 are listed in FIG. **17**.

pCNR1, pCNR2, pCNR3, and pCNR4

The sequence encoding the full length 16 cysteines (16C) mature protein (without the leader peptide and GPI addition sequence) was PCR amplified from the *P. falciparum* line 3D7 using the primers 5'-CACC GGA TCC GGA AAC AAT GAT TTT TGT AAG CCT AGC 3' (nucleotides 79-105) (counting from A in the ATG start codon of Pfs48/45) and 5'-GGA TCC CTA TGC TGA ATC TAT AGT AAC TGT CAT ATA AGC 3'(nucleotides 1255-1284). The sequence encoding the C-terminal 10 cysteine part (10C) was PCR amplified using the primers 5'-CACC GGA TCC GAT AAT ACT GAA AAG GTT ATA TCA AGT ATA (nucleotides 475-504) and 5'-GGA TCC CTA TGC TGA ATC TAT AGT AAC TGT CAT ATA AGC 3' (nucleotides 1255-1284). The sequence encoding the N-terminal 6 cysteine part (6N) was amplified using the primers 5'-CACC GGA TCC GGA AAC AAT GAT TTT TGT AAG CCT AGC 3' (nucleotides 79-105) and 5'-GGA TCC CTA AGC ACT TCT CCC TTC TAT ACT TGA 3' (nucleotides 496-519). Finally, the sequence encoding the

N-terminal 10 cysteine part (10N) was amplified using the primers 5'-CACC GGA TCC GGA AAC AAT GAT TTT TGT AAG CCT AGC 3' (nucleotides 79-105) and 5'-GGA TCC CTA TCC GTG TAT GAC TTT TTT TTC ATA 3' (nucleotides 868-891). The BamHI restriction sites in the primers are underlined and the artificial STOP codons are in bold. Following digestion with BamHI (New England Biolabs), the amplified DNA fragments were inserted into (i): BglII digested pPSM1013, resulting in the plasmids pCNR1 (Pfs45/48_16C), pCNR2 (Pfs45/48_10C), pCNR3 (Pfs45/48_6N), and, pCNR4 (Pfs45/48_10N) or (ii) BglII digested pAMJ219, resulting in the plasmids pCNR9 (Pfs45/48_16C), pCNR10 (Pfs45/48_10C), pCNR11 (Pfs45/48_6N), and, pCNR12 (Pfs45/48_10N).

pCNR5, pCNR6, pCNR7, and, pCNR8

Plasmids pCNR1, pCNR2, pCNR3, and, pCNR4 were digested with BamHI and SalI, and the resulting DNA fragments containing the Pfs45/48-16C, -10C, -6N and, -10N inserts, were cloned into BamHI-SalI digested pAMJ328.

Culture Conditions

All flask experiments were carried out at 30° C. without shaking or an active supply of air. Each flask, containing 300 ml *L. lactis* media supplemented with 1% (w/v) glucose and 10 ng/ml of erythromycin, were inoculated with 3 ml of a fresh overnight culture grown in the same medium. Cultures were grown until approximately two h after the stationary phase had been reached. Growth was monitored by measuring the OD_{600} every ½-1 h.

Product Analysis, SDS-PAGE, and Immunoblotting

For product analysis, 5 ml of *L. lactis* cultures collected 2 h after cells had entered the stationary phase were harvested by centrifugation at 4° C. and 8000×g for 5 min. The culture supernatants and cells were processed separately. Supernatants were filtered on 0.2-μm-pore-size filters and trichloroacetic acid (TCA) (5% final concentration) was added to the culture filtrate and incubated at 4° C. over night. Following centrifugation (4° C. and 15.000×g for 20 min) the resulting pellets were redissolved in 15 μl of SDS sample buffer. Intracellular and cell-associated proteins were prepared by the method of Le Loir et al. (14). Briefly, cell pellets were washed once with 1 ml of ice-cold TES (25% sucrose, 1 mM EDTA, 50 mM Tris-HCL; pH 8), resuspended in TES and precipitated with TCA (10% final concentration). Cell pellets were then washed once with 1 ml of ice cold acetone, dried, and resuspended in 70 μl of TES containing lysozyme (1 mg/ml). After 30 min of incubation at 37° C., cells were lysed with 30 μl of 20% SDS. SDS-PAGE was performed according to Laemmli (13) using the Xcell SureLock mini-cell system (Invitrogen). Samples were boiled for 5 min and separated on 4-12% Tris-glycine gels from Invitrogen according to the manufacturer. The proteins were either Coomassie stained or electroblotted onto nitrocellulose membranes using the Xcell II blot module (Invitrogen). Nitrocellulose membranes were blocked in Tris buffer (50 mM Tris-HCl [pH 8], 0.15 M NaCl) containing 1% BSA. A polyclonal serum raised against Pfs45/48 in rabbits (dilution 1:100) and rat monoclonal antibodies raised against the Pfs45/48 epitope V (code nr: 85RF45.5) (dilution 1:1000) was kindly provided by N. Outchkourov, Radboud University, The Netherlands Immunodetection was performed with alkaline-phosphatase-coupled swine anti-rabbit antibodies (dilution 1:1000) (Dako) and alkaline-phosphatase-coupled goat anti-rat antibodies (dilution 1:30.000) (Sigma).

Example 6

Fusions between GLURP-R0 (R0), MSP3, and Fragments of Pfs48/45

In an attempt to increase the yield of correctly folded Pfs48/45 protein, a range of new fusions between GLURP-R0 (R0), MSP3, and carefully selected fragments of Pfs48/45 containing either 10 cysteine (10C) or 6 cysteine (6C) residues were screened in the 2-sided ELISA after fermentation at the 1 L scale.

The Pfs48/45 fragments where selected so they contained epitope I (domaine III in FIG. **1**) or the epitope I, II and III (domaine II & III) e.g. the 6C homologues (6Ca, 6Cb, 6Cc, 6Cd) and the 10C homologues (10Ca, 10Cb, 10Cc, 10Cd) in table 7. The amino acid sequence (AA) and the nucleic acid sequence (bp) of the homologues in table 7 refer to the sequence numbers in SEQ ID NO 3 and 4 respectively.

TABLE 7

Various homologues of 10C and 6C fragments fused in frame to either GLURP.R0 or GLURP.R0-MSP3

Name	Start in Pfs48/45 (AA)	Start in Pfs48/45 (bp)	Stop in Pfs48/45 (AA)	Stop in Pfs48/45 (bp)
10Ca	D159	475	A428	1284
10Cb	D159	475	A419	1257
10Cc	P200	598	A428	1284
10Cd	P200	598	A419	1257
6Ca	K287	859	A419	1284
6Cb	K287	859	A419	1257
6Cc	A292	871	A419	1284
6Cd	A292	871	A419	1257

The yield of the culture supernatant of the Pfs48/45 fragments/homologues fused to GLURP.R0-MSP3 is given in table 8

TABLE 8

Name	Yield mg/L
10Ca	39
10Cb	38
10Cc	56
10Cd	30
6Ca	32
6Cb	43
6Cc	50
6Cd	26

One of these, R0.MSP3.6 Cc proved to have enhanced intrinsic structural properties allowing for better protein folding and a high yield. R0.MSP3.6 Cc, produces 30-60 mg recombinant protein per L culture supernatant, of which ~35% is correctly folded. Preliminary data suggests that it is feasible to purify 100% correctly folded R0.6 Cc using conventional purification methods. The purification was done in three steps. Step 1: Purification on a Hitrap crude FF Ni^{++}-column where raw culture supernatant was adjusted to pH 7.4, applied to the column, and eluted with 500 mM Imidazole; binding efficiency is approx 65% (FIG. **18**A, table 9). Step 2: Size exclusion chromatography on a Superdex 200S. The eluate from step 1 was applied to a Superdex 200S column and eluted in two overlapping peaks. Peak 1 contains predominantly multimers and peak 2 contains predominantly monomer. Approximately 55% of peak 2 is correctly folded (FIG. **18**B, table 9). Step 3: Ion exchange chromatography on Q HP. The monomer fraction from step 2 was applied to a Q HP column and bound protein was eluted with a gradient of NaCl in the column buffer. Two overlapping peaks are apparent. Peak 1 contains ~100% correctly folded monomer (FIG. **18**C, table 9).

This represents a significant increase in correctly folded protein species as compared to R0.10C.

TABLE 9

Potency of R0.MSP3.6Cc at each step.

Sample	Total yield of R0.6Cc (mg)	Potency[a] (%)	Yield of correctly folded R0.6Cc (mg)
Culture supernatant	50	35	17.5
Step 1	35	35	12.6
Step 2 (peak 2)	9	55	5
Step 3 (peak 1)	4.5	100	4.5

[a]The 100% correctly folded R0.10C is used as a reference for estimating the amount of correctly folded R0.6Cc. By using this reference we assume that the affinity of mAb 45.1 for epitope 1 encoded by R0.10C is similar to the affinity for epitope 1 encoded by the R0.6Cc construct.

Example 7

Production of other CYRP Proteins

In addition to the described Pfs48/45 protein fusions, we have created a set of protein fusions between GLURP.R0 and cysteine-rich domains of Var2CSA, Var4, and EBA175. As for R0.10C and R0.6 Cc, these chimera accumulate in *L. lactis* culture supernatants as monomeric recombinant proteins.

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SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 28

<210> SEQ ID NO 1
<211> LENGTH: 1271
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 1

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            20                  25                  30

Lys Arg Ile Gly Gly Pro Lys Leu Arg Gly Asn Val Thr Ser Asn Ile
        35                  40                  45

Lys Phe Pro Ser Asp Asn Lys Gly Lys Ile Ile Arg Gly Ser Asn Asp
    50                  55                  60

Lys Leu Asn Lys Asn Ser Glu Asp Val Leu Glu Gln Ser Glu Lys Ser
65                  70                  75                  80

Leu Val Ser Glu Asn Val Pro Ser Gly Leu Asp Ile Asp Asp Ile Pro
                85                  90                  95

Lys Glu Ser Ile Phe Ile Gln Glu Asp Gln Glu Gly Gln Thr His Ser
            100                 105                 110

Glu Leu Asn Pro Glu Thr Ser Glu His Ser Lys Asp Leu Asn Asn Asn
        115                 120                 125

Gly Ser Lys Asn Glu Ser Ser Asp Ile Ile Ser Glu Asn Asn Lys Ser
    130                 135                 140

Asn Lys Val Gln Asn His Phe Glu Ser Leu Ser Asp Leu Glu Leu Leu
145                 150                 155                 160

Glu Asn Ser Ser Gln Asp Asn Leu Asp Lys Asp Thr Ile Ser Thr Glu
                165                 170                 175

Pro Phe Pro Asn Gln Lys His Lys Asp Leu Gln Gln Asp Leu Asn Asp
            180                 185                 190

Glu Pro Leu Glu Pro Phe Pro Thr Gln Ile His Lys Asp Tyr Lys Glu
        195                 200                 205

Lys Asn Leu Ile Asn Glu Glu Asp Ser Glu Pro Phe Pro Arg Gln Lys
    210                 215                 220

His Lys Lys Val Asp Asn His Asn Glu Glu Lys Asn Val Phe His Glu
225                 230                 235                 240

Asn Gly Ser Ala Asn Gly Asn Gln Gly Ser Leu Lys Leu Lys Ser Phe
                245                 250                 255

Asp Glu His Leu Lys Asp Glu Lys Ile Glu Asn Glu Pro Leu Val His
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           260                 265                 270

Glu Asn Leu Ser Ile Pro Asn Asp Pro Ile Glu Gln Ile Leu Asn Gln
        275                 280                 285

Pro Glu Gln Glu Thr Asn Ile Gln Glu Gln Leu Tyr Asn Glu Lys Gln
    290                 295                 300

Asn Val Glu Glu Lys Gln Asn Ser Gln Ile Pro Ser Leu Asp Leu Lys
305                 310                 315                 320

Glu Pro Thr Asn Glu Asp Ile Leu Pro Asn His Asn Pro Leu Glu Asn
                325                 330                 335

Ile Lys Gln Ser Glu Ser Glu Ile Asn His Val Gln Asp His Ala Leu
            340                 345                 350

Pro Lys Glu Asn Ile Ile Asp Lys Leu Asp Asn Gln Lys Glu His Ile
        355                 360                 365

Asp Gln Ser Gln His Asn Ile Asn Val Leu Gln Glu Asn Asn Ile Asn
    370                 375                 380

Asn His Gln Leu Glu Pro Gln Glu Lys Pro Asn Ile Glu Ser Phe Glu
385                 390                 395                 400

Pro Lys Asn Ile Asp Ser Glu Ile Ile Leu Pro Glu Asn Val Glu Thr
                405                 410                 415

Glu Glu Ile Ile Asp Asp Val Pro Ser Pro Lys His Ser Asn His Glu
            420                 425                 430

Thr Phe Glu Glu Glu Thr Ser Glu Ser Glu His Glu Glu Ala Val Ser
        435                 440                 445

Glu Lys Asn Ala His Glu Thr Val Glu His Glu Glu Thr Val Ser Gln
    450                 455                 460

Glu Ser Asn Pro Glu Lys Ala Asp Asn Asp Gly Asn Val Ser Gln Asn
465                 470                 475                 480

Ser Asn Asn Glu Leu Asn Glu Asn Glu Phe Val Glu Ser Glu Lys Ser
                485                 490                 495

Glu His Glu Ala Ala Glu Asn Glu Glu Ser Ser Leu Glu Glu Gly His
            500                 505                 510

His Glu Glu Ile Val Pro Glu Gln Asn Asn Glu Glu Ser Gly Glu Ser
        515                 520                 525

Lys Leu Val Asp Asn Asp Glu Gly Gly Phe Glu Glu Ala His His Glu
    530                 535                 540

Asn Phe Ser Ser Glu Val Ser Asn Ser Glu Leu Asn Glu Asn Glu Phe
545                 550                 555                 560

Val Glu Ser Asp Lys Ser Val Thr Glu Pro Ala Glu His Glu Glu Val
                565                 570                 575

Val Ser Glu Glu Ser Asn Pro Glu Pro Ala Glu Asn Glu Glu Ser Ser
            580                 585                 590

Ile Glu Glu Ala His Gln Glu Glu Ile Val Pro Glu Gln Asn Asp Glu
        595                 600                 605

Glu Ser Gly Glu Ser Gly Leu Val Asp Asn Glu Glu Gly Asp Phe Glu
    610                 615                 620

Glu Pro Asn His Glu Glu Phe Glu Pro Asp Gln Asn Asp Ser Glu Leu
625                 630                 635                 640

Ser Glu Asn Glu Leu Val Glu Ser Glu Lys Ser Val Ser Glu Pro Ala
                645                 650                 655

Glu His Val Glu Ile Val Ser Glu Lys Ser Val Ser Glu Pro Ala Glu
            660                 665                 670

His Val Glu Ile Val Ser Glu Lys Ser Thr Ser Glu Pro Ala Glu His
        675                 680                 685
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Val Glu Ser Val Ser Glu Gln Ser Asn Asn Glu Pro Ser Glu Lys Lys
    690                 695                 700

Asp Gly Pro Val Pro Ser Lys Pro Phe Glu Glu Ile Glu Lys Val Asp
705                 710                 715                 720

Val Gln Pro Lys Ile Val Asp Leu Gln Ile Ile Glu Pro Asn Phe Val
                725                 730                 735

Asp Ser Gln Pro Asn Pro Gln Glu Pro Val Glu Pro Ser Phe Val Lys
            740                 745                 750

Ile Glu Lys Val Pro Ser Glu Glu Asn Lys His Ala Ser Val Asp Pro
        755                 760                 765

Glu Val Lys Glu Lys Glu Asn Val Ser Glu Val Val Glu Glu Lys Gln
    770                 775                 780

Asn Ser Gln Glu Ser Val Glu Glu Ile Pro Val Asn Glu Asp Glu Phe
785                 790                 795                 800

Glu Asp Val His Thr Glu Gln Leu Asp Leu Asp His Lys Thr Val Asp
                805                 810                 815

Pro Glu Ile Val Glu Val Glu Glu Ile Pro Ser Glu Leu His Glu Asn
            820                 825                 830

Glu Val Ala His Pro Glu Ile Val Glu Ile Glu Glu Val Phe Pro Glu
        835                 840                 845

Pro Asn Gln Asn Asn Glu Phe Gln Glu Ile Asn Glu Asp Asp Lys Ser
    850                 855                 860

Ala His Ile Gln His Glu Ile Val Glu Val Glu Glu Ile Leu Pro Glu
865                 870                 875                 880

Asp Asp Lys Asn Glu Lys Val Glu His Glu Ile Val Glu Val Glu Glu
                885                 890                 895

Ile Leu Pro Glu Asp Lys Asn Glu Lys Gly Gln His Glu Ile Val Glu
            900                 905                 910

Val Glu Glu Ile Leu Pro Glu Asp Asp Lys Asn Glu Lys Val Glu His
        915                 920                 925

Glu Ile Val Glu Val Glu Glu Ile Leu Pro Glu Asp Lys Asn Glu Lys
    930                 935                 940

Gly Gln His Glu Ile Val Glu Val Glu Glu Ile Leu Pro Glu Asp Lys
945                 950                 955                 960

Asn Glu Lys Val Glu His Glu Ile Val Glu Val Glu Glu Ile Leu Pro
                965                 970                 975

Glu Asp Lys Asn Glu Lys Gly Gln His Glu Ile Val Glu Val Glu Glu
            980                 985                 990

Ile Leu Pro Glu Asp Lys Asn Glu  Lys Val Gln His Glu  Ile Val Glu
        995                 1000                1005

Val Glu  Glu Ile Leu Pro Glu  Asp Lys Asn Glu Lys  Gly Gln His
    1010                1015                1020

Glu Ile  Val Glu Val Glu Glu  Ile Leu Pro Glu Glu  Asp Lys Asn
    1025                1030                1035

Glu Lys  Gly Gln His Glu Ile  Val Glu Val Glu Glu  Ile Leu Pro
    1040                1045                1050

Glu Asp  Lys Asn Glu Lys Val  Gln His Glu Ile Val  Glu Val Glu
    1055                1060                1065

Glu Ile  Leu Pro Glu Asp Lys  Asn Glu Lys Val Gln  His Glu Ile
    1070                1075                1080

Val Glu  Val Glu Glu Ile Leu  Pro Glu Ile Val Glu  Ile Glu Glu
    1085                1090                1095
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Val Pro  Ser Gln Thr Asn Asn  Asn Glu Asn Ile Glu  Thr Ile Lys
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Pro Glu  Glu Lys Lys Asn Glu  Phe Ser Val Glu Glu  Lys Ala Ile
    1115                1120                1125

Pro Gln  Glu Pro Val Val Pro  Thr Leu Asn Glu Asn  Glu Asn Val
    1130                1135                1140

Thr Pro  Lys Pro Ser Glu Gly  Glu Ser Thr Lys Pro  Asp Ile Val
    1145                1150                1155

Gln Ile  Lys Ile Val Gln Glu  Asn Lys Pro Asn Lys  Lys Glu Thr
    1160                1165                1170

Pro Val  Val Asp Gly Pro Lys  His Val Glu Gln Asn  Ile Gln Glu
    1175                1180                1185

Asp Asp  Asn Asp Glu Glu Asp  Asp Asp Asp Ile Asp  Phe Glu Gly
    1190                1195                1200

Leu Ser  Arg Lys Asp Asp Glu  Lys Asp Ser Ser Asn  Lys Asn Lys
    1205                1210                1215

Lys Lys  Ser Ser Phe Ile Thr  Tyr Ile Ser Thr Lys  Lys Phe Lys
    1220                1225                1230

Lys Val  Ser Gln Thr Ile Val  Ser Val Met Ile Asn  Ala Tyr Asp
    1235                1240                1245

Gly Val  Ile Gln Val Val Ser  Thr Ile Lys Gly Ile  Ala Lys Asp
    1250                1255                1260

Ile Val  Ile Phe Phe Gln Asn  Ile
    1265                1270


<210> SEQ ID NO 2
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<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

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aggggtaatg ttacaagtaa tataaagttc ccatcagata acaaaggtaa aattataaga    180

ggttcgaatg ataaacttaa taaaaactct gaagatgttt tagaacaaag cgaaaaatcg    240

cttgtttcag aaaatgttcc tagtggatta gatatagatg atatccctaa agaatctatt    300

tttattcaag aagatcaaga aggtcaaact cattctgaat taaatcctga aacatcagaa    360

catagtaaag atttaaataa taatggttca aaaaatgaat ctagtgatat tatttcagaa    420

aataataaat caaataaagt acaaaatcat tttgaatcat tatcagattt agaattactt    480

gaaaattcct cacaagataa tttagacaaa gatacaattt caacagaacc ttttcctaat    540

caaaaacata aagacttaca acaagattta aatgatgaac ctttagaacc ctttcctaca    600

caaatacata aagattataa agaaaaaaat ttaataaatg aagaagattc agaaccattt    660

cccagacaaa agcataaaaa ggtagacaat cataatgaag aaaaaaacgt atttcatgaa    720

aatggttctg caaatggtaa tcaaggaagt ttgaaactta aatcattcga tgaacattta    780

aaagatgaaa aaatagaaaa tgaaccactt gttcatgaaa atttatccat accaaatgat    840

ccaatagaac aaatattaaa tcaacctgaa caagaaacaa atatccagga acaattgtat    900

aatgaaaaac aaaatgttga agaaaaacaa aattctcaaa taccttcgtt agatttaaaa    960

gaaccaacaa atgaagatat tttaccaaat cataatccat tagaaaatat aaaacaaagt   1020

gaatcagaaa taaatcatgt acaagatcat gcgctaccaa aagagaatat aatagacaaa   1080
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cctaaaaata tagattcaga aattattctt cctgaaaatg ttgaaacaga agaaataata 1260

gatgatgtgc cttcccctaa acattctaac catgaaacat ttgaagaaga aacaagtgaa 1320

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gctgaaaatg aagaaagtag tcttgaagaa ggccatcatg aagaaattgt acctgaacaa 1560

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catgtagaac aaaatataca agaagatgat aatgatgaag aggatgatga tgatatagat 3600

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tcatctttta taacatatat atctacaaag aaatttaaaa aagtatctca aactattgta 3720

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<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

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Tyr Ile Val Leu Val Leu Arg Ile Ile Ser Gly Asn Asn Asp Phe Cys
20 25 30

Lys Pro Ser Ser Leu Asn Ser Glu Ile Ser Gly Phe Ile Gly Tyr Lys
35 40 45

Cys Asn Phe Ser Asn Glu Gly Val His Asn Leu Lys Pro Asp Met Arg
50 55 60

Glu Arg Arg Ser Ile Phe Cys Thr Ile His Ser Tyr Phe Ile Tyr Asp
65 70 75 80

Lys Ile Arg Leu Ile Ile Pro Lys Lys Ser Ser Ser Pro Glu Phe Lys
85 90 95

Ile Leu Pro Glu Lys Cys Phe Gln Lys Val Tyr Thr Asp Tyr Glu Asn
100 105 110

Arg Val Glu Thr Asp Ile Ser Glu Leu Gly Leu Ile Glu Tyr Glu Ile
115 120 125

Glu Glu Asn Asp Thr Asn Pro Asn Tyr Asn Glu Arg Thr Ile Thr Ile
130 135 140

Ser Pro Phe Ser Pro Lys Asp Ile Glu Phe Phe Cys Phe Cys Asp Asn
145 150 155 160

Thr Glu Lys Val Ile Ser Ser Ile Glu Gly Arg Ser Ala Met Val His
165 170 175

Val Arg Val Leu Lys Tyr Pro His Asn Ile Leu Phe Thr Asn Leu Thr
180 185 190

Asn Asp Leu Phe Thr Tyr Leu Pro Lys Thr Tyr Asn Glu Ser Asn Phe
195 200 205

Val Ser Asn Val Leu Glu Val Glu Leu Asn Asp Gly Glu Leu Phe Val
210 215 220

Leu Ala Cys Glu Leu Ile Asn Lys Lys Cys Phe Gln Glu Gly Lys Glu
225 230 235 240

Lys Ala Leu Tyr Lys Ser Asn Lys Ile Ile Tyr His Lys Asn Leu Thr
245 250 255

Ile Phe Lys Ala Pro Phe Tyr Val Thr Ser Lys Asp Val Asn Thr Glu
260 265 270

Cys Thr Cys Lys Phe Lys Asn Asn Asn Tyr Lys Ile Val Leu Lys Pro
275 280 285

Lys Tyr Glu Lys Lys Val Ile His Gly Cys Asn Phe Ser Ser Asn Val
290 295 300

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Ser Ser Lys His Thr Phe Thr Asp Ser Leu Asp Ile Ser Leu Val Asp
305                 310                 315                 320

Asp Ser Ala His Ile Ser Cys Asn Val His Leu Ser Glu Pro Lys Tyr
                325                 330                 335

Asn His Leu Val Gly Leu Asn Cys Pro Gly Asp Ile Ile Pro Asp Cys
            340                 345                 350

Phe Phe Gln Val Tyr Gln Pro Glu Ser Glu Glu Leu Glu Pro Ser Asn
        355                 360                 365

Ile Val Tyr Leu Asp Ser Gln Ile Asn Ile Gly Asp Ile Glu Tyr Tyr
    370                 375                 380

Glu Asp Ala Glu Gly Asp Asp Lys Ile Lys Leu Phe Gly Ile Val Gly
385                 390                 395                 400

Ser Ile Pro Lys Thr Thr Ser Phe Thr Cys Ile Cys Lys Lys Asp Lys
                405                 410                 415

Lys Ser Ala Tyr Met Thr Val Thr Ile Asp Ser Ala Tyr Tyr Gly Phe
            420                 425                 430

Leu Ala Lys Thr Phe Ile Phe Leu Ile Val Ala Ile Leu Leu Tyr Ile
        435                 440                 445
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<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 4

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atatctggat tcataggata taagtgtaat ttttcaaatg aaggtgttca taatttaaag    180

ccagatatgc gtgaacgtag gtctattttt tgcaccatcc attcgtattt tatatatgat    240

aagataagat taataatacc taaaaaaagt tcgtctcctg agtttaaaat attaccagaa    300

aaatgttttc aaaaagtata tactgattat gagaatagag ttgaaactga tatatcggaa    360

ttaggtttaa ttgaatatga aatagaagaa aatgatacaa accctaatta taatgaaagg    420

acaataacta tatctccatt tagtccaaaa gacattgaat ttttttgttt ttgtgataat    480

actgaaaagg ttatatcaag tatagaaggg agaagtgcta tggtacatgt acgtgtatta    540

aaatatccac ataatatttt atttactaat ttaacaaatg atctttttac atatttgccg    600

aaaacatata atgaatctaa ttttgtaagt aatgtattag aagtagaatt gaatgatgga    660

gaattatttg ttttagcttg tgaactaatt aataaaaaat gttttcaaga aggaaaagaa    720

aaagccttat ataaaagtaa taaaataatt tatcataaaa acttaactat ctttaaagct    780

ccattttatg ttacatcaaa agatgttaat acagaatgta catgcaaatt taaaaataat    840

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ggtttaaatt gtcctggtga tattatacca gattgctttt ttcaagtata tcaacctgaa   1080

tcagaagaac ttgaaccatc caacattgtt tatttagatt cacaaataaa tataggagat   1140

attgaatatt atgaagatgc tgaaggagat gataaaatta aattatttgg tatagttgga   1200

agtataccaa aaacgacatc ttttacttgt atatgtaaga aggataaaaa aagtgcttat   1260

atgacagtta ctatagattc agcatattat ggatttttgg ctaaaacatt tatattccta   1320
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attgtagcaa tattattata tatttag 1347

<210> SEQ ID NO 5
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<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

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Lys Leu Arg Gly Asn Val Thr Ser Asn Ile Lys Phe Pro Ser Asp Asn
20 25 30

Lys Gly Lys Ile Ile Arg Gly Ser Asn Asp Lys Leu Asn Lys Asn Ser
35 40 45

Glu Asp Val Leu Glu Gln Ser Glu Lys Ser Leu Val Ser Glu Asn Val
50 55 60

Pro Ser Gly Leu Asp Ile Asp Asp Ile Pro Lys Glu Ser Ile Phe Ile
65 70 75 80

Gln Glu Asp Gln Glu Gly Gln Thr His Ser Glu Leu Asn Pro Glu Thr
85 90 95

Ser Glu His Ser Lys Asp Leu Asn Asn Asn Gly Ser Lys Asn Glu Ser
100 105 110

Ser Asp Ile Ile Ser Glu Asn Asn Lys Ser Asn Lys Val Gln Asn His
115 120 125

Phe Glu Ser Leu Ser Asp Leu Glu Leu Leu Glu Asn Ser Ser Gln Asp
130 135 140

Asn Leu Asp Lys Asp Thr Ile Ser Thr Glu Pro Phe Pro Asn Gln Lys
145 150 155 160

His Lys Asp Leu Gln Gln Asp Leu Asn Asp Glu Pro Leu Glu Pro Phe
165 170 175

Pro Thr Gln Ile His Lys Asp Tyr Lys Glu Lys Asn Leu Ile Asn Glu
180 185 190

Glu Asp Ser Glu Pro Phe Pro Arg Gln Lys His Lys Lys Val Asp Asn
195 200 205

His Asn Glu Glu Lys Asn Val Phe His Glu Asn Gly Ser Ala Asn Gly
210 215 220

Asn Gln Gly Ser Leu Lys Leu Lys Ser Phe Asp Glu His Leu Lys Asp
225 230 235 240

Glu Lys Ile Glu Asn Glu Pro Leu Val His Glu Asn Leu Ser Ile Pro
245 250 255

Asn Asp Pro Ile Glu Gln Ile Leu Asn Gln Pro Glu Gln Glu Thr Asn
260 265 270

Ile Gln Glu Gln Leu Tyr Asn Glu Lys Gln Asn Val Glu Glu Lys Gln
275 280 285

Asn Ser Gln Ile Pro Ser Leu Asp Leu Lys Glu Pro Thr Asn Glu Asp
290 295 300

Ile Leu Pro Asn His Asn Pro Leu Glu Asn Ile Lys Gln Ser Glu Ser
305 310 315 320

Glu Ile Asn His Val Gln Asp His Ala Leu Pro Lys Glu Asn Ile Ile
325 330 335

Asp Lys Leu Asp Asn Gln Lys Glu His Ile Asp Gln Ser Gln His Asn
340 345 350

Ile Asn Val Leu Gln Glu Asn Asn Ile Asn Asn His Gln Leu Glu Pro
355 360 365

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Gln Glu Lys Pro Asn Ile Glu Ser Phe Glu Pro Lys Asn Ile Asp Ser
    370                 375                 380

Glu Ile Ile Leu Pro Glu Asn Val Glu Thr Glu Glu Ile Ile Asp Asp
385                 390                 395                 400

Val Pro Ser Pro Lys His Ser Asn His Glu Thr Phe Glu Glu Glu Thr
                405                 410                 415

Ser Glu Ser Glu His Glu Glu Ala Val Ser Glu Lys Asn Ala His Glu
            420                 425                 430

Thr Val Glu His Glu Glu Thr Val Ser Gln Glu Ser Asn Pro Glu Lys
        435                 440                 445

Ala Asp Asn Asp Gly Asn Val Ser Gln Asn Ser Asn Asn Glu Leu Asn
    450                 455                 460

Glu Asn Glu Phe Val Glu Ser Glu Lys Ser Glu His Glu Ala Asp Asn
465                 470                 475                 480

Thr Glu Lys Val Ile Ser Ser Ile Glu Gly Arg Ser Ala Met Val His
                485                 490                 495

Val Arg Val Leu Lys Tyr Pro His Asn Ile Leu Phe Thr Asn Leu Thr
            500                 505                 510

Asn Asp Leu Phe Thr Tyr Leu Pro Lys Thr Tyr Asn Glu Ser Asn Phe
        515                 520                 525

Val Ser Asn Val Leu Glu Val Glu Leu Asn Asp Gly Glu Leu Phe Val
    530                 535                 540

Leu Ala Cys Glu Leu Ile Asn Lys Lys Cys Phe Gln Glu Gly Lys Glu
545                 550                 555                 560

Lys Ala Leu Tyr Lys Ser Asn Lys Ile Ile Tyr His Lys Asn Leu Thr
                565                 570                 575

Ile Phe Lys Ala Pro Phe Tyr Val Thr Ser Lys Asp Val Asn Thr Glu
            580                 585                 590

Cys Thr Cys Lys Phe Lys Asn Asn Asn Tyr Lys Ile Val Leu Lys Pro
        595                 600                 605

Lys Tyr Glu Lys Lys Val Ile His Gly Cys Asn Phe Ser Ser Asn Val
    610                 615                 620

Ser Ser Lys His Thr Phe Thr Asp Ser Leu Asp Ile Ser Leu Val Asp
625                 630                 635                 640

Asp Ser Ala His Ile Ser Cys Asn Val His Leu Ser Glu Pro Lys Tyr
                645                 650                 655

Asn His Leu Val Gly Leu Asn Cys Pro Gly Asp Ile Ile Pro Asp Cys
            660                 665                 670

Phe Phe Gln Val Tyr Gln Pro Glu Ser Glu Glu Leu Glu Pro Ser Asn
        675                 680                 685

Ile Val Tyr Leu Asp Ser Gln Ile Asn Ile Gly Asp Ile Glu Tyr Tyr
    690                 695                 700

Glu Asp Ala Glu Gly Asp Asp Lys Ile Lys Leu Phe Gly Ile Val Gly
705                 710                 715                 720

Ser Ile Pro Lys Thr Thr Ser Phe Thr Cys Ile Cys Lys Lys Asp Lys
                725                 730                 735

Lys Ser Ala Tyr Met Thr Val Thr Ile Asp Ser Ala His His His His
            740                 745                 750

His His
```

<210> SEQ ID NO 6
<211> LENGTH: 2361
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

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<400> SEQUENCE: 6

atgaaattta ataaaaaaag agttgcaata gccacgttta ttgctttgat atttgtaagt 60

ttttttacaa tatcatcaat ccaagatgct caagcagccg aaagatctac aagtgagaat 120

agaaataaac gaatcggggg tcctaaatta aggggtaatg ttacaagtaa tataaagttc 180

ccatcagata acaaaggtaa aattataaga ggttcgaatg ataaacttaa taaaaactct 240

gaagatgttt tagaacaaag cgaaaaatcg cttgtttcag aaaatgttcc tagtggatta 300

gatatagatg atatccctaa agaatctatt tttattcaag aagatcaaga aggtcaaact 360

cattctgaat taaatcctga aacatcagaa catagtaaag atttaaataa taatggttca 420

aaaaatgaat ctagtgatat tatttcagaa aataataaat caaataaagt acaaaatcat 480

tttgaatcat tatcagattt agaattactt gaaaattcct cacaagataa tttagacaaa 540

gatacaattt caacagaacc ttttcctaat caaaaacata aagacttaca acaagattta 600

aatgatgaac ctttagaacc ctttcctaca caaatacata aagattataa agaaaaaaat 660

ttaataaatg aagaagattc agaaccattt cccagacaaa agcataaaaa ggtagacaat 720

cataatgaag aaaaaaacgt atttcatgaa aatggttctg caaatggtaa tcaaggaagt 780

ttgaaactta aatcattcga tgaacattta aaagatgaaa aaatagaaaa tgaaccactt 840

gttcatgaaa atttatccat accaaatgat ccaatagaac aaatattaaa tcaacctgaa 900

caagaaacaa atatccagga acaattgtat aatgaaaaac aaaatgttga agaaaaacaa 960

aattctcaaa taccttcgtt agatttaaaa gaaccaacaa atgaagatat tttaccaaat 1020

cataatccat tagaaaatat aaaacaaagt gaatcagaaa taaatcatgt acaagatcat 1080

gcgctaccaa aagagaatat aatagacaaa cttgataatc aaaaagaaca catcgatcaa 1140

tcacaacata atataaatgt attacaagaa aataacataa acaatcacca attagaacct 1200

caagagaaac ctaatattga atcgtttgaa cctaaaaata tagattcaga aattattctt 1260

cctgaaaatg ttgaaacaga agaaataata gatgatgtgc cttcccctaa acattctaac 1320

catgaaacat ttgaagaaga aacaagtgaa tctgaacatg aagaagccgt atctgaaaaa 1380

aatgcccacg aaactgtcga acatgaagaa actgtgtctc aagaaagcaa tcctgaaaaa 1440

gctgataatg atggaaatgt atctcaaaac agcaacaacg aattaaatga aaatgaattc 1500

gttgaatcgg aaaaaagcga gcatgaagca gataatactg aaaaggttat atcaagtata 1560

gaagggagaa gtgctatggt acatgtacgt gtattaaaat atccacataa tattttattt 1620

actaatttaa caaatgatct ttttacatat ttgccgaaaa catataatga atctaatttt 1680

gtaagtaatg tattagaagt agaattgaat gatggagaat tatttgtttt agcttgtgaa 1740

ctaattaata aaaaatgttt tcaagaagga aaagaaaaag ccttatataa aagtaataaa 1800

ataatttatc ataaaaactt aactatcttt aaagctccat tttatgttac atcaaaagat 1860

gttaatacag aatgtacatg caaatttaaa aataataatt ataaaatagt tttaaaacca 1920

aaatatgaaa aaaaagtcat acacggatgt aacttctctt caaatgttag ttctaaacat 1980

acttttacag atagtttaga tatttcttta gttgatgata gtgcacatat ttcatgtaac 2040

gtacatttgt ctgaaccaaa atataatcat ttggtaggtt taaattgtcc tggtgatatt 2100

ataccagatt gctttttttca agtatatcaa cctgaatcag aagaacttga accatccaac 2160

attgtttatt tagattcaca aataaatata ggagatattg aatattatga agatgctgaa 2220

ggagatgata aaattaaatt atttggtata gttggaagta taccaaaaac gacatctttt 2280

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acttgtatat gtaagaagga taaaaaaagt gcttatatga cagttactat agattcagca 2340

catcaccatc atcaccatta g 2361

<210> SEQ ID NO 7
<211> LENGTH: 875
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 7

Ala Glu Arg Ser Thr Ser Glu Asn Arg Asn Lys Arg Ile Gly Gly Pro
1 5 10 15

Lys Leu Arg Gly Asn Val Thr Ser Asn Ile Lys Phe Pro Ser Asp Asn
20 25 30

Lys Gly Lys Ile Ile Arg Gly Ser Asn Asp Lys Leu Asn Lys Asn Ser
35 40 45

Glu Asp Val Leu Glu Gln Ser Glu Lys Ser Leu Val Ser Glu Asn Val
50 55 60

Pro Ser Gly Leu Asp Ile Asp Asp Ile Pro Lys Glu Ser Ile Phe Ile
65 70 75 80

Gln Glu Asp Gln Glu Gly Gln Thr His Ser Glu Leu Asn Pro Glu Thr
85 90 95

Ser Glu His Ser Lys Asp Leu Asn Asn Asn Gly Ser Lys Asn Glu Ser
100 105 110

Ser Asp Ile Ile Ser Glu Asn Asn Lys Ser Asn Lys Val Gln Asn His
115 120 125

Phe Glu Ser Leu Ser Asp Leu Glu Leu Leu Glu Asn Ser Ser Gln Asp
130 135 140

Asn Leu Asp Lys Asp Thr Ile Ser Thr Glu Pro Phe Pro Asn Gln Lys
145 150 155 160

His Lys Asp Leu Gln Gln Asp Leu Asn Asp Glu Pro Leu Glu Pro Phe
165 170 175

Pro Thr Gln Ile His Lys Asp Tyr Lys Glu Lys Asn Leu Ile Asn Glu
180 185 190

Glu Asp Ser Glu Pro Phe Pro Arg Gln Lys His Lys Lys Val Asp Asn
195 200 205

His Asn Glu Glu Lys Asn Val Phe His Glu Asn Gly Ser Ala Asn Gly
210 215 220

Asn Gln Gly Ser Leu Lys Leu Lys Ser Phe Asp Glu His Leu Lys Asp
225 230 235 240

Glu Lys Ile Glu Asn Glu Pro Leu Val His Glu Asn Leu Ser Ile Pro
245 250 255

Asn Asp Pro Ile Glu Gln Ile Leu Asn Gln Pro Glu Gln Glu Thr Asn
260 265 270

Ile Gln Glu Gln Leu Tyr Asn Glu Lys Gln Asn Val Glu Glu Lys Gln
275 280 285

Asn Ser Gln Ile Pro Ser Leu Asp Leu Lys Glu Pro Thr Asn Glu Asp
290 295 300

Ile Leu Pro Asn His Asn Pro Leu Glu Asn Ile Lys Gln Ser Glu Ser
305 310 315 320

Glu Ile Asn His Val Gln Asp His Ala Leu Pro Lys Glu Asn Ile Ile
325 330 335

Asp Lys Leu Asp Asn Gln Lys Glu His Ile Asp Gln Ser Gln His Asn
340 345 350

Ile Asn Val Leu Gln Glu Asn Asn Ile Asn Asn His Gln Leu Glu Pro

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        355                 360                 365

Gln Glu Lys Pro Asn Ile Glu Ser Phe Glu Pro Lys Asn Ile Asp Ser
    370                 375                 380

Glu Ile Ile Leu Pro Glu Asn Val Glu Thr Glu Glu Ile Ile Asp Asp
385                 390                 395                 400

Val Pro Ser Pro Lys His Ser Asn His Glu Thr Phe Glu Glu Glu Thr
                405                 410                 415

Ser Glu Ser Glu His Glu Glu Ala Val Ser Glu Lys Asn Ala His Glu
            420                 425                 430

Thr Val Glu His Glu Glu Thr Val Ser Gln Glu Ser Asn Pro Glu Lys
        435                 440                 445

Ala Asp Asn Asp Gly Asn Val Ser Gln Asn Ser Asn Asn Glu Leu Asn
    450                 455                 460

Glu Asn Glu Phe Val Glu Ser Glu Lys Ser Glu His Glu Ala Gly Asn
465                 470                 475                 480

Asn Asp Phe Cys Lys Pro Ser Ser Leu Asn Ser Glu Ile Ser Gly Phe
                485                 490                 495

Ile Gly Tyr Lys Cys Asn Phe Ser Asn Glu Gly Val His Asn Leu Lys
            500                 505                 510

Pro Asp Met Arg Glu Arg Arg Ser Ile Phe Cys Thr Ile His Ser Tyr
        515                 520                 525

Phe Ile Tyr Asp Lys Ile Arg Leu Ile Ile Pro Lys Lys Ser Ser Ser
    530                 535                 540

Pro Glu Phe Lys Ile Leu Pro Glu Lys Cys Phe Gln Lys Val Tyr Thr
545                 550                 555                 560

Asp Tyr Glu Asn Arg Val Glu Thr Asp Ile Ser Glu Leu Gly Leu Ile
                565                 570                 575

Glu Tyr Glu Ile Glu Glu Asn Asp Thr Asn Pro Asn Tyr Asn Glu Arg
            580                 585                 590

Thr Ile Thr Ile Ser Pro Phe Ser Pro Lys Asp Ile Glu Phe Phe Cys
        595                 600                 605

Phe Cys Asp Asn Thr Glu Lys Val Ile Ser Ser Ile Glu Gly Arg Ser
    610                 615                 620

Ala Met Val His Val Arg Val Leu Lys Tyr Pro His Asn Ile Leu Phe
625                 630                 635                 640

Thr Asn Leu Thr Asn Asp Leu Phe Thr Tyr Leu Pro Lys Thr Tyr Asn
                645                 650                 655

Glu Ser Asn Phe Val Ser Asn Val Leu Glu Val Glu Leu Asn Asp Gly
            660                 665                 670

Glu Leu Phe Val Leu Ala Cys Glu Leu Ile Asn Lys Lys Cys Phe Gln
        675                 680                 685

Glu Gly Lys Glu Lys Ala Leu Tyr Lys Ser Asn Lys Ile Ile Tyr His
    690                 695                 700

Lys Asn Leu Thr Ile Phe Lys Ala Pro Phe Tyr Val Thr Ser Lys Asp
705                 710                 715                 720

Val Asn Thr Glu Cys Thr Cys Lys Phe Lys Asn Asn Asn Tyr Lys Ile
                725                 730                 735

Val Leu Lys Pro Lys Tyr Glu Lys Lys Val Ile His Gly Cys Asn Phe
            740                 745                 750

Ser Ser Asn Val Ser Ser Lys His Thr Phe Thr Asp Ser Leu Asp Ile
        755                 760                 765

Ser Leu Val Asp Asp Ser Ala His Ile Ser Cys Asn Val His Leu Ser
    770                 775                 780
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Glu Pro Lys Tyr Asn His Leu Val Gly Leu Asn Cys Pro Gly Asp Ile
785                 790                 795                 800

Ile Pro Asp Cys Phe Phe Gln Val Tyr Gln Pro Glu Ser Glu Glu Leu
                805                 810                 815

Glu Pro Ser Asn Ile Val Tyr Leu Asp Ser Gln Ile Asn Ile Gly Asp
            820                 825                 830

Ile Glu Tyr Tyr Glu Asp Ala Glu Gly Asp Asp Lys Ile Lys Leu Phe
        835                 840                 845

Gly Ile Val Gly Ser Ile Pro Lys Thr Thr Ser Phe Thr Cys Ile Cys
    850                 855                 860

Lys Lys Asp Lys Lys His His His His His His
865                 870                 875


<210> SEQ ID NO 8
<211> LENGTH: 2724
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 8

atgaaattta ataaaaaaag agttgcaata gccacgttta ttgctttgat atttgtaagt     60

ttttttacaa tatcatcaat ccaagatgct caagcagccg aaagatctac aagtgagaat    120

agaaataaac gaatcggggg tcctaaatta aggggtaatg ttacaagtaa tataaagttc    180

ccatcagata acaaaggtaa aattataaga ggttcgaatg ataaacttaa taaaaactct    240

gaagatgttt tagaacaaag cgaaaaatcg cttgtttcag aaaatgttcc tagtggatta    300

gatatagatg atatccctaa agaatctatt tttattcaag aagatcaaga aggtcaaact    360

cattctgaat taaatcctga aacatcagaa catagtaaag atttaaataa taatggttca    420

aaaaatgaat ctagtgatat tatttcagaa aataataaat caaataaagt acaaaatcat    480

tttgaatcat tatcagattt agaattactt gaaaattcct cacaagataa tttagacaaa    540

gatacaattt caacagaacc ttttcctaat caaaaacata aagacttaca acaagattta    600

aatgatgaac ctttagaacc ctttcctaca caaatacata aagattataa agaaaaaaat    660

ttaataaatg aagaagattc agaaccattt cccagacaaa agcataaaaa ggtagacaat    720

cataatgaag aaaaaaacgt atttcatgaa aatggttctg caaatggtaa tcaaggaagt    780

ttgaaactta aatcattcga tgaacattta aaagatgaaa aaatagaaaa tgaaccactt    840

gttcatgaaa atttatccat accaaatgat ccaatagaac aaatattaaa tcaacctgaa    900

caagaaacaa atatccagga acaattgtat aatgaaaaac aaaatgttga agaaaaacaa    960

aattctcaaa taccttcgtt agatttaaaa gaaccaacaa atgaagatat tttaccaaat   1020

cataatccat tagaaaatat aaaacaaagt gaatcagaaa taaatcatgt acaagatcat   1080

gcgctaccaa aagagaatat aatagacaaa cttgataatc aaaaagaaca catcgatcaa   1140

tcacaacata atataaatgt attacaagaa aataacataa acaatcacca attagaacct   1200

caagagaaac ctaatattga atcgtttgaa cctaaaaata tagattcaga aattattctt   1260

cctgaaaatg ttgaaacaga agaaataata gatgatgtgc cttcccctaa acattctaac   1320

catgaaacat ttgaagaaga aacaagtgaa tctgaacatg aagaagccgt atctgaaaaa   1380

aatgcccacg aaactgtcga acatgaagaa actgtgtctc aagaaagcaa tcctgaaaaa   1440

gctgataatg atggaaatgt atctcaaaac agcaacaacg aattaaatga aaatgaattc   1500

gttgaatcgg aaaaaagcga gcatgaagca ggaaacaatg atttttgtaa gcctagctct   1560
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ttgaatagtg aaatatctgg attcatagga tataagtgta atttttcaaa tgaaggtgtt   1620

cataatttaa agccagatat gcgtgaacgt aggtctattt tttgcaccat ccattcgtat   1680

tttatatatg ataagataag attaataata cctaaaaaaa gttcgtctcc tgagtttaaa   1740

atattaccag aaaaatgttt tcaaaaagta tatactgatt atgagaatag agttgaaact   1800

gatatatcgg aattaggttt aattgaatat gaaatagaag aaaatgatac aaaccctaat   1860

tataatgaaa ggacaataac tatatctcca tttagtccaa aagacattga atttttttgt   1920

ttttgtgata atactgaaaa ggttatatca agtatagaag ggagaagtgc tatggtacat   1980

gtacgtgtat taaaatatcc acataatatt ttatttacta atttaacaaa tgatcttttt   2040

acatatttgc cgaaaacata taatgaatct aattttgtaa gtaatgtatt agaagtagaa   2100

ttgaatgatg gagaattatt tgttttagct tgtgaactaa ttaataaaaa atgttttcaa   2160

gaaggaaaag aaaaagcctt atataaaagt aataaaataa tttatcataa aaacttaact   2220

atctttaaag ctccatttta tgttacatca aaagatgtta atacagaatg tacatgcaaa   2280

tttaaaaata ataattataa aatagtttta aaaccaaaat atgaaaaaaa agtcatacac   2340

ggatgtaact tctcttcaaa tgttagttct aaacatactt ttacagatag tttagatatt   2400

tctttagttg atgatagtgc acatatttca tgtaacgtac atttgtctga accaaaatat   2460

aatcatttgg taggtttaaa ttgtcctggt gatattatac cagattgctt ttttcaagta   2520

tatcaacctg aatcagaaga acttgaacca tccaacattg tttatttaga ttcacaaata   2580

aatataggag atattgaata ttatgaagat gctgaaggag atgataaaat taaattattt   2640

ggtatagttg gaagtatacc aaaaacgaca tcttttactt gtatatgtaa gaaggataaa   2700

aaacatcacc atcatcacca ttag                                          2724
```

<210> SEQ ID NO 9
<211> LENGTH: 641
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 9

```
Ala Glu Arg Ser Ser Ser Asp Ile Ile Ser Glu Asn Asn Lys Ser Asn
1               5                   10                  15

Lys Val Gln Asn His Phe Glu Ser Leu Ser Asp Leu Glu Leu Leu Glu
            20                  25                  30

Asn Ser Ser Gln Asp Asn Leu Asp Lys Asp Thr Ile Ser Thr Glu Pro
        35                  40                  45

Phe Pro Asn Gln Lys His Lys Asp Leu Gln Gln Asp Leu Asn Asp Glu
    50                  55                  60

Pro Leu Glu Pro Phe Pro Thr Gln Ile His Lys Asp Tyr Lys Glu Lys
65                  70                  75                  80

Asn Leu Ile Asn Glu Glu Asp Ser Glu Pro Phe Pro Arg Gln Lys His
                85                  90                  95

Lys Lys Val Asp Asn His Asn Glu Glu Lys Asn Val Phe His Glu Asn
            100                 105                 110

Gly Ser Ala Asn Gly Asn Gln Gly Ser Leu Lys Leu Lys Ser Phe Asp
        115                 120                 125

Glu His Leu Lys Asp Glu Lys Ile Glu Asn Glu Pro Leu Val His Glu
    130                 135                 140

Asn Leu Ser Ile Pro Asn Asp Pro Ile Glu Gln Ile Leu Asn Gln Pro
145                 150                 155                 160

Glu Gln Glu Thr Asn Ile Gln Glu Gln Leu Tyr Asn Glu Lys Gln Asn
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                165                 170                 175

Val Glu Glu Lys Gln Asn Ser Gln Ile Pro Ser Leu Asp Leu Lys Glu
            180                 185                 190

Pro Thr Asn Glu Asp Ile Leu Pro Asn His Asn Pro Leu Glu Asn Ile
        195                 200                 205

Lys Gln Ser Glu Ser Glu Ile Asn His Val Gln Asp His Ala Leu Pro
    210                 215                 220

Lys Glu Asn Ile Ile Asp Lys Leu Asp Asn Gln Lys Glu His Ile Asp
225                 230                 235                 240

Gln Ser Gln His Asn Ile Asn Val Leu Gln Glu Asn Asn Ile Asn Asn
                245                 250                 255

His Gln Leu Glu Pro Gln Glu Lys Pro Asn Ile Glu Ser Phe Glu Pro
            260                 265                 270

Lys Asn Ile Asp Ser Glu Ile Ile Leu Pro Glu Asn Val Glu Thr Glu
        275                 280                 285

Glu Ile Ile Asp Asp Val Pro Ser Pro Lys His Ser Asn His Glu Thr
    290                 295                 300

Phe Glu Glu Glu Thr Ser Glu Ser Glu His Glu Glu Ala Val Ser Glu
305                 310                 315                 320

Lys Asn Ala His Glu Thr Val Glu His Glu Glu Thr Val Ser Gln Glu
                325                 330                 335

Ser Asn Pro Glu Lys Ala Asp Asn Asp Gly Asn Val Ser Gln Asn Ser
            340                 345                 350

Asn Asn Glu Leu Asn Glu Asn Glu Phe Val Glu Ser Glu Lys Ser Glu
        355                 360                 365

His Glu Ala Asp Asn Thr Glu Lys Val Ile Ser Ser Ile Glu Gly Arg
    370                 375                 380

Ser Ala Met Val His Val Arg Val Leu Lys Tyr Pro His Asn Ile Leu
385                 390                 395                 400

Phe Thr Asn Leu Thr Asn Asp Leu Phe Thr Tyr Leu Pro Lys Thr Tyr
                405                 410                 415

Asn Glu Ser Asn Phe Val Ser Asn Val Leu Glu Val Glu Leu Asn Asp
            420                 425                 430

Gly Glu Leu Phe Val Leu Ala Cys Glu Leu Ile Asn Lys Lys Cys Phe
        435                 440                 445

Gln Glu Gly Lys Glu Lys Ala Leu Tyr Lys Ser Asn Lys Ile Ile Tyr
    450                 455                 460

His Lys Asn Leu Thr Ile Phe Lys Ala Pro Phe Tyr Val Thr Ser Lys
465                 470                 475                 480

Asp Val Asn Thr Glu Cys Thr Cys Lys Phe Lys Asn Asn Asn Tyr Lys
                485                 490                 495

Ile Val Leu Lys Pro Lys Tyr Glu Lys Lys Val Ile His Gly Cys Asn
            500                 505                 510

Phe Ser Ser Asn Val Ser Ser Lys His Thr Phe Thr Asp Ser Leu Asp
        515                 520                 525

Ile Ser Leu Val Asp Asp Ser Ala His Ile Ser Cys Asn Val His Leu
    530                 535                 540

Ser Glu Pro Lys Tyr Asn His Leu Val Gly Leu Asn Cys Pro Gly Asp
545                 550                 555                 560

Ile Ile Pro Asp Cys Phe Phe Gln Val Tyr Gln Pro Glu Ser Glu Glu
                565                 570                 575

Leu Glu Pro Ser Asn Ile Val Tyr Leu Asp Ser Gln Ile Asn Ile Gly
            580                 585                 590
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Asp Ile Glu Tyr Tyr Glu Asp Ala Glu Gly Asp Asp Lys Ile Lys Leu
        595                 600                 605

Phe Gly Ile Val Gly Ser Ile Pro Lys Thr Thr Ser Phe Thr Cys Ile
    610                 615                 620

Cys Lys Lys Asp Lys Lys Ser Ala Tyr Met Thr Val Thr Ile Asp Ser
625                 630                 635                 640

Ala
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<210> SEQ ID NO 10
<211> LENGTH: 2289
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 10

```
atgaaattta ataaaaaaag agttgcaata gccacgttta ttgctttgat atttgtaagt     60

ttttttacaa tatcatcaat ccaagatgct caagcagccg aaagatctac aagtaatata    120

aagttcccat cagataacaa aggtaaaatt ataagaggtt cgaatgataa acttaataaa    180

aactctgaag atgttttaga acaaagcgaa aaatcgcttg tttcagaaaa tgttcctagt    240

ggattagata tagatgatat ccctaaagaa tctatttttа ttcaagaaga tcaagaaggt    300

caaactcatt ctgaattaaa tcctgaaaca tcagaacata gtaaagattt aaataataat    360

ggttcaaaaa atgaatctag tgatattatt tcagaaaata ataaatcaaa taaagtacaa    420

aatcattttg aatcattatc agatttagaa ttacttgaaa attcctcaca agataattta    480

gacaaagata caatttcaac agaaccttttt cctaatcaaa aacataaaga cttacaacaa    540

gatttaaatg atgaaccttt agaacccttt cctacacaaa tacataaaga ttataaagaa    600

aaaaatttaa taaatgaaga agattcagaa ccatttccca gacaaaagca taaaaaggta    660

gacaatcata atgaagaaaa aaacgtattt catgaaaatg gttctgcaaa tggtaatcaa    720

ggaagtttga aacttaaatc attcgatgaa catttaaaag atgaaaaaat agaaaatgaa    780

ccacttgttc atgaaaattt atccatacca aatgatccaa tagaacaaat attaaatcaa    840

cctgaacaag aaacaaatat ccaggaacaa ttgtataatg aaaaacaaaa tgttgaagaa    900

aaacaaaatt ctcaaatacc ttcgttagat ttaaaagaac caacaaatga agatatttta    960

ccaaatcata atccattaga aaatataaaa caaagtgaat cagaaataaa tcatgtacaa   1020

gatcatgcgc taccaaaaga gaatataata gacaaacttg ataatcaaaa agaacacatc   1080

gatcaatcac aacataatat aaatgtatta caagaaaata acataaacaa tcaccaatta   1140

gaacctcaag agaaacctaa tattgaatcg tttgaaccta aaaatataga ttcagaaatt   1200

attcttcctg aaaatgttga aacagaagaa ataatagatg atgtgccttc ccctaaacat   1260

tctaaccatg aaacatttga agaagaaaca agtgaatctg aacatgaaga agccgtatct   1320

gaaaaaaatg cccacgaaac tgtcgaacat gaagaaactg tgtctcaaga aagcaatcct   1380

gaaaaagctg ataatgatgg aaatgtatct caaaacagca acaacgaatt aaatgaaaat   1440

gaattcgttg aatcggaaaa aagcgagcat gaagcagata atactgaaaa ggttatatca   1500

agtatagaag ggagaagtgc tatggtacat gtacgtgtat taaaatatcc acataatatt   1560

ttatttacta atttaacaaa tgatcttttt acatatttgc cgaaaacata taatgaatct   1620

aattttgtaa gtaatgtatt agaagtagaa ttgaatgatg gagaattatt tgttttagct   1680

tgtgaactaa ttaataaaaa atgttttcaa gaaggaaaag aaaaagcctt atataaaagt   1740

aataaaataa tttatcataa aaacttaact atctttaaag ctccatttta tgttacatca   1800
```

-continued

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aaagatgtta atacagaatg tacatgcaaa tttaaaaata ataattataa aatagtttta   1860

aaaccaaaat atgaaaaaaa agtcatacac ggatgtaact tctcttcaaa tgttagttct   1920

aaacatactt ttacagatag tttagatatt tctttagttg atgatagtgc acatatttca   1980

tgtaacgtac atttgtctga accaaaatat aatcatttgg taggtttaaa ttgtcctggt   2040

gatattatac cagattgctt ttttcaagta tatcaacctg aatcagaaga acttgaacca   2100

tccaacattg tttatttaga ttcacaaata aatataggag atattgaata ttatgaagat   2160

gctgaaggag atgataaaat taaattattt ggtatagttg gaagtatacc aaaaacgaca   2220

tcttttactt gtatatgtaa gaaggataaa aaaagtgctt atatgacagt tactatagat   2280

tcagcatag                                                          2289
```

<210> SEQ ID NO 11
<211> LENGTH: 762
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 11

```
Ala Glu Arg Ser Ser Ser Asp Ile Ile Ser Glu Asn Asn Lys Ser Asn
1               5                   10                  15

Lys Val Gln Asn His Phe Glu Ser Leu Ser Asp Leu Glu Leu Leu Glu
            20                  25                  30

Asn Ser Ser Gln Asp Asn Leu Asp Lys Asp Thr Ile Ser Thr Glu Pro
        35                  40                  45

Phe Pro Asn Gln Lys His Lys Asp Leu Gln Gln Asp Leu Asn Asp Glu
    50                  55                  60

Pro Leu Glu Pro Phe Pro Thr Gln Ile His Lys Asp Tyr Lys Glu Lys
65                  70                  75                  80

Asn Leu Ile Asn Glu Glu Asp Ser Glu Pro Phe Pro Arg Gln Lys His
                85                  90                  95

Lys Lys Val Asp Asn His Asn Glu Glu Lys Asn Val Phe His Glu Asn
            100                 105                 110

Gly Ser Ala Asn Gly Asn Gln Gly Ser Leu Lys Leu Lys Ser Phe Asp
        115                 120                 125

Glu His Leu Lys Asp Glu Lys Ile Glu Asn Glu Pro Leu Val His Glu
    130                 135                 140

Asn Leu Ser Ile Pro Asn Asp Pro Ile Glu Gln Ile Leu Asn Gln Pro
145                 150                 155                 160

Glu Gln Glu Thr Asn Ile Gln Glu Gln Leu Tyr Asn Glu Lys Gln Asn
                165                 170                 175

Val Glu Glu Lys Gln Asn Ser Gln Ile Pro Ser Leu Asp Leu Lys Glu
            180                 185                 190

Pro Thr Asn Glu Asp Ile Leu Pro Asn His Asn Pro Leu Glu Asn Ile
        195                 200                 205

Lys Gln Ser Glu Ser Glu Ile Asn His Val Gln Asp His Ala Leu Pro
    210                 215                 220

Lys Glu Asn Ile Ile Asp Lys Leu Asp Asn Gln Lys Glu His Ile Asp
225                 230                 235                 240

Gln Ser Gln His Asn Ile Asn Val Leu Gln Glu Asn Asn Ile Asn Asn
                245                 250                 255

His Gln Leu Glu Pro Gln Glu Lys Pro Asn Ile Glu Ser Phe Glu Pro
            260                 265                 270

Lys Asn Ile Asp Ser Glu Ile Ile Leu Pro Glu Asn Val Glu Thr Glu
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        275                 280                 285

Glu Ile Ile Asp Asp Val Pro Ser Pro Lys His Ser Asn His Glu Thr
    290                 295                 300

Phe Glu Glu Glu Thr Ser Glu Ser Glu His Glu Glu Ala Val Ser Glu
305                 310                 315                 320

Lys Asn Ala His Glu Thr Val Glu His Glu Glu Thr Val Ser Gln Glu
                325                 330                 335

Ser Asn Pro Glu Lys Ala Asp Asn Asp Gly Asn Val Ser Gln Asn Ser
            340                 345                 350

Asn Asn Glu Leu Asn Glu Asn Glu Phe Val Glu Ser Glu Lys Ser Glu
        355                 360                 365

His Glu Ala Gly Asn Asn Asp Phe Cys Lys Pro Ser Ser Leu Asn Ser
    370                 375                 380

Glu Ile Ser Gly Phe Ile Gly Tyr Lys Cys Asn Phe Ser Asn Glu Gly
385                 390                 395                 400

Val His Asn Leu Lys Pro Asp Met Arg Glu Arg Arg Ser Ile Phe Cys
                405                 410                 415

Thr Ile His Ser Tyr Phe Ile Tyr Asp Lys Ile Arg Leu Ile Ile Pro
            420                 425                 430

Lys Lys Ser Ser Ser Pro Glu Phe Lys Ile Leu Pro Glu Lys Cys Phe
        435                 440                 445

Gln Lys Val Tyr Thr Asp Tyr Glu Asn Arg Val Glu Thr Asp Ile Ser
    450                 455                 460

Glu Leu Gly Leu Ile Glu Tyr Glu Ile Glu Glu Asn Asp Thr Asn Pro
465                 470                 475                 480

Asn Tyr Asn Glu Arg Thr Ile Thr Ile Ser Pro Phe Ser Pro Lys Asp
                485                 490                 495

Ile Glu Phe Phe Cys Phe Cys Asp Asn Thr Glu Lys Val Ile Ser Ser
            500                 505                 510

Ile Glu Gly Arg Ser Ala Met Val His Val Arg Val Leu Lys Tyr Pro
        515                 520                 525

His Asn Ile Leu Phe Thr Asn Leu Thr Asn Asp Leu Phe Thr Tyr Leu
    530                 535                 540

Pro Lys Thr Tyr Asn Glu Ser Asn Phe Val Ser Asn Val Leu Glu Val
545                 550                 555                 560

Glu Leu Asn Asp Gly Glu Leu Phe Val Leu Ala Cys Glu Leu Ile Asn
                565                 570                 575

Lys Lys Cys Phe Gln Glu Gly Lys Glu Lys Ala Leu Tyr Lys Ser Asn
            580                 585                 590

Lys Ile Ile Tyr His Lys Asn Leu Thr Ile Phe Lys Ala Pro Phe Tyr
        595                 600                 605

Val Thr Ser Lys Asp Val Asn Thr Glu Cys Thr Cys Lys Phe Lys Asn
    610                 615                 620

Asn Asn Tyr Lys Ile Val Leu Lys Pro Lys Tyr Glu Lys Lys Val Ile
625                 630                 635                 640

His Gly Cys Asn Phe Ser Ser Asn Val Ser Ser Lys His Thr Phe Thr
                645                 650                 655

Asp Ser Leu Asp Ile Ser Leu Val Asp Asp Ser Ala His Ile Ser Cys
            660                 665                 670

Asn Val His Leu Ser Glu Pro Lys Tyr Asn His Leu Val Gly Leu Asn
        675                 680                 685

Cys Pro Gly Asp Ile Ile Pro Asp Cys Phe Phe Gln Val Tyr Gln Pro
    690                 695                 700
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Glu Ser Glu Glu Leu Glu Pro Ser Asn Ile Val Tyr Leu Asp Ser Gln
705                 710                 715                 720

Ile Asn Ile Gly Asp Ile Glu Tyr Tyr Glu Asp Ala Glu Gly Asp Asp
                725                 730                 735

Lys Ile Lys Leu Phe Gly Ile Val Gly Ser Ile Pro Lys Thr Thr Ser
            740                 745                 750

Phe Thr Cys Ile Cys Lys Lys Asp Lys Lys
        755                 760
```

<210> SEQ ID NO 12
<211> LENGTH: 2652
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 12

```
atgaaattta ataaaaaaag agttgcaata gccacgttta ttgctttgat atttgtaagt     60

ttttttacaa tatcatcaat ccaagatgct caagcagccg aaagatctac aagtaatata    120

aagttcccat cagataacaa aggtaaaatt ataagaggtt cgaatgataa acttaataaa    180

aactctgaag atgttttaga acaaagcgaa aaatcgcttg tttcagaaaa tgttcctagt    240

ggattagata tagatgatat ccctaaagaa tctatttttа ttcaagaaga tcaagaaggt    300

caaactcatt ctgaattaaa tcctgaaaca tcagaacata gtaaagattt aaataataat    360

ggttcaaaaa atgaatctag tgatattatt tcagaaaata ataaatcaaa taaagtacaa    420

aatcattttg aatcattatc agatttagaa ttacttgaaa attcctcaca agataattta    480

gacaaagata caatttcaac agaacctttt cctaatcaaa aacataaaga cttacaacaa    540

gatttaaatg atgaaccttt agaaccttt cctacacaaa tacataaaga ttataaagaa    600

aaaaatttaa taaatgaaga agattcagaa ccatttccca gacaaaagca taaaaaggta    660

gacaatcata atgaagaaaa aaacgtattt catgaaaatg gttctgcaaa tggtaatcaa    720

ggaagtttga aacttaaatc attcgatgaa catttaaaag atgaaaaaat agaaaatgaa    780

ccacttgttc atgaaaattt atccatacca aatgatccaa tagaacaaat attaaatcaa    840

cctgaacaag aaacaaatat ccaggaacaa ttgtataatg aaaaacaaaa tgttgaagaa    900

aaacaaaatt ctcaaatacc ttcgttagat ttaaaagaac caacaaatga agatatttta    960

ccaaatcata atccattaga aaatataaaa caaagtgaat cagaaataaa tcatgtacaa   1020

gatcatgcgc taccaaaaga gaatataata gacaaacttg ataatcaaaa agaacacatc   1080

gatcaatcac aacataatat aaatgtatta caagaaaata acataaacaa tcaccaatta   1140

gaacctcaag agaaacctaa tattgaatcg tttgaaccta aaaatataga ttcagaaatt   1200

attcttcctg aaaatgttga aacagaagaa ataatagatg atgtgccttc ccctaaacat   1260

tctaaccatg aaacatttga agaagaaaca agtgaatctg aacatgaaga agccgtatct   1320

gaaaaaaatg cccacgaaac tgtcgaacat gaagaaactg tgtctcaaga aagcaatcct   1380

gaaaaagctg ataatgatgg aaatgtatct caaaacagca acaacgaatt aaatgaaaat   1440

gaattcgttg aatcggaaaa aagcgagcat gaagcaggaa acaatgattt ttgtaagcct   1500

agctctttga atagtgaaat atctggattc ataggatata agtgtaattt ttcaaatgaa   1560

ggtgttcata atttaaagcc agatatgcgt gaacgtaggt ctatttttтg caccatccat   1620

tcgtatttta tatatgataa gataagatta ataataccta aaaaaagttc gtctcctgag   1680

tttaaaatat taccagaaaa atgttttcaa aaagtatata ctgattatga gaatagagtt   1740
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gaaactgata tatcggaatt aggtttaatt gaatatgaaa tagaagaaaa tgatacaaac 1800

cctaattata atgaaaggac aataactata tctccattta gtccaaaaga cattgaattt 1860

ttttgttttt gtgataatac tgaaaaggtt atatcaagta tagaagggag aagtgctatg 1920

gtacatgtac gtgtattaaa atatccacat aatattttat ttactaattt aacaaatgat 1980

ctttttacat atttgccgaa aacatataat gaatctaatt ttgtaagtaa tgtattagaa 2040

gtagaattga atgatggaga attatttgtt ttagcttgtg aactaattaa taaaaaatgt 2100

tttcaagaag gaaaagaaaa agccttatat aaaagtaata aaataattta tcataaaaac 2160

ttaactatct ttaaagctcc attttatgtt acatcaaaag atgttaatac agaatgtaca 2220

tgcaaattta aaaataataa ttataaaata gttttaaaac caaaatatga aaaaaaagtc 2280

atacacggat gtaacttctc ttcaaatgtt agttctaaac atacttttac agatagttta 2340

gatatttctt tagttgatga tagtgcacat atttcatgta acgtacattt gtctgaacca 2400

aaatataatc atttggtagg tttaaattgt cctggtgata ttataccaga ttgctttttt 2460

caagtatatc aacctgaatc agaagaactt gaaccatcca acattgttta tttagattca 2520

caaataaata taggagatat tgaatattat gaagatgctg aaggagatga taaaattaaa 2580

ttatttggta tagttggaag tataccaaaa acgacatctt ttacttgtat atgtaagaag 2640

gataaaaaat ag 2652

<210> SEQ ID NO 13
<211> LENGTH: 1502
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 13

Met Lys Cys Asn Ile Ser Ile Tyr Phe Phe Ala Ser Phe Phe Val Leu
1 5 10 15

Tyr Phe Ala Lys Ala Arg Asn Glu Tyr Asp Ile Lys Glu Asn Glu Lys
20 25 30

Phe Leu Asp Val Tyr Lys Glu Lys Phe Asn Glu Leu Asp Lys Lys Lys
35 40 45

Tyr Gly Asn Val Gln Lys Thr Asp Lys Lys Ile Phe Thr Phe Ile Glu
50 55 60

Asn Lys Leu Asp Ile Leu Asn Asn Ser Lys Phe Asn Lys Arg Trp Lys
65 70 75 80

Ser Tyr Gly Thr Pro Asp Asn Ile Asp Lys Asn Met Ser Leu Ile Asn
85 90 95

Lys His Asn Asn Glu Glu Met Phe Asn Asn Asn Tyr Gln Ser Phe Leu
100 105 110

Ser Thr Ser Ser Leu Ile Lys Gln Asn Lys Tyr Val Pro Ile Asn Ala
115 120 125

Val Arg Val Ser Arg Ile Leu Ser Phe Leu Asp Ser Arg Ile Asn Asn
130 135 140

Gly Arg Asn Thr Ser Ser Asn Asn Glu Val Leu Ser Asn Cys Arg Glu
145 150 155 160

Lys Arg Lys Gly Met Lys Trp Asp Cys Lys Lys Lys Asn Asp Arg Ser
165 170 175

Asn Tyr Val Cys Ile Pro Asp Arg Arg Ile Gln Leu Cys Ile Val Asn
180 185 190

Leu Ser Ile Ile Lys Thr Tyr Thr Lys Glu Thr Met Lys Asp His Phe
195 200 205

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Ile Glu Ala Ser Lys Lys Glu Ser Gln Leu Leu Leu Lys Lys Asn Asp
    210                 215                 220

Asn Lys Tyr Asn Ser Lys Phe Cys Asn Asp Leu Lys Asn Ser Phe Leu
225                 230                 235                 240

Asp Tyr Gly His Leu Ala Met Gly Asn Asp Met Asp Phe Gly Gly Tyr
                245                 250                 255

Ser Thr Lys Ala Glu Asn Lys Ile Gln Glu Val Phe Lys Gly Ala His
            260                 265                 270

Gly Glu Ile Ser Glu His Lys Ile Lys Asn Phe Arg Lys Lys Trp Trp
        275                 280                 285

Asn Glu Phe Arg Glu Lys Leu Trp Glu Ala Met Leu Ser Glu His Lys
    290                 295                 300

Asn Asn Ile Asn Asn Cys Lys Asn Ile Pro Gln Glu Glu Leu Gln Ile
305                 310                 315                 320

Thr Gln Trp Ile Lys Glu Trp His Gly Glu Phe Leu Leu Glu Arg Asp
                325                 330                 335

Asn Arg Ser Lys Leu Pro Lys Ser Lys Cys Lys Asn Asn Thr Leu Tyr
            340                 345                 350

Glu Ala Cys Glu Lys Glu Cys Ile Asp Pro Cys Met Lys Tyr Arg Asp
        355                 360                 365

Trp Ile Ile Arg Ser Lys Phe Glu Trp His Thr Leu Ser Lys Glu Tyr
    370                 375                 380

Glu Thr Gln Lys Val Pro Lys Glu Asn Ala Glu Asn Tyr Leu Ile Lys
385                 390                 395                 400

Ile Ser Glu Asn Lys Asn Asp Ala Lys Val Ser Leu Leu Leu Asn Asn
                405                 410                 415

Cys Asp Ala Glu Tyr Ser Lys Tyr Cys Asp Cys Lys His Thr Thr Thr
            420                 425                 430

Leu Val Lys Ser Val Leu Asn Gly Asn Asp Asn Thr Ile Lys Glu Lys
        435                 440                 445

Arg Glu His Ile Asp Leu Asp Asp Phe Ser Lys Phe Gly Cys Asp Lys
    450                 455                 460

Asn Ser Val Asp Thr Asn Thr Lys Val Trp Glu Cys Lys Lys Pro Tyr
465                 470                 475                 480

Lys Leu Ser Thr Lys Asp Val Cys Val Pro Pro Arg Arg Gln Glu Leu
                485                 490                 495

Cys Leu Gly Asn Ile Asp Arg Ile Tyr Asp Lys Asn Leu Leu Met Ile
            500                 505                 510

Lys Glu His Ile Leu Ala Ile Ala Ile Tyr Glu Ser Arg Ile Leu Lys
        515                 520                 525

Arg Lys Tyr Lys Asn Lys Asp Asp Lys Glu Val Cys Lys Ile Ile Asn
    530                 535                 540

Lys Thr Phe Ala Asp Ile Arg Asp Ile Ile Gly Gly Thr Asp Tyr Trp
545                 550                 555                 560

Asn Asp Leu Ser Asn Arg Lys Leu Val Gly Lys Ile Asn Thr Asn Ser
                565                 570                 575

Asn Tyr Val His Arg Asn Lys Gln Asn Asp Lys Leu Phe Arg Asp Glu
            580                 585                 590

Trp Trp Lys Val Ile Lys Lys Asp Val Trp Asn Val Ile Ser Trp Val
        595                 600                 605

Phe Lys Asp Lys Thr Val Cys Lys Glu Asp Asp Ile Glu Asn Ile Pro
    610                 615                 620

Gln Phe Phe Arg Trp Phe Ser Glu Trp Gly Asp Asp Tyr Cys Gln Asp
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625                 630                 635                 640

Lys Thr Lys Met Ile Glu Thr Leu Lys Val Glu Cys Lys Glu Lys Pro
                645                 650                 655

Cys Glu Asp Asp Asn Cys Lys Arg Lys Cys Asn Ser Tyr Lys Glu Trp
            660                 665                 670

Ile Ser Lys Lys Lys Glu Glu Tyr Asn Lys Gln Ala Lys Gln Tyr Gln
        675                 680                 685

Glu Tyr Gln Lys Gly Asn Asn Tyr Lys Met Tyr Ser Glu Phe Lys Ser
    690                 695                 700

Ile Lys Pro Glu Val Tyr Leu Lys Lys Tyr Ser Glu Lys Cys Ser Asn
705                 710                 715                 720

Leu Asn Phe Glu Asp Glu Phe Lys Glu Glu Leu His Ser Asp Tyr Lys
                725                 730                 735

Asn Lys Cys Thr Met Cys Pro Glu Val Lys Asp Val Pro Ile Ser Ile
            740                 745                 750

Ile Arg Asn Asn Glu Gln Thr Ser Gln Glu Ala Val Pro Glu Glu Ser
        755                 760                 765

Thr Glu Ile Ala His Arg Thr Glu Thr Arg Thr Asp Glu Arg Lys Asn
    770                 775                 780

Gln Glu Pro Ala Asn Lys Asp Leu Lys Asn Pro Gln Gln Ser Val Gly
785                 790                 795                 800

Glu Asn Gly Thr Lys Asp Leu Leu Gln Glu Asp Leu Gly Gly Ser Arg
                805                 810                 815

Ser Glu Asp Glu Val Thr Gln Glu Phe Gly Val Asn His Gly Ile Pro
            820                 825                 830

Lys Gly Glu Asp Gln Thr Leu Gly Lys Ser Asp Ala Ile Pro Asn Ile
        835                 840                 845

Gly Glu Pro Glu Thr Gly Ile Ser Thr Thr Glu Glu Ser Arg His Glu
    850                 855                 860

Glu Gly His Asn Lys Gln Ala Leu Ser Thr Ser Val Asp Glu Pro Glu
865                 870                 875                 880

Leu Ser Asp Thr Leu Gln Leu His Glu Asp Thr Lys Glu Asn Asp Lys
                885                 890                 895

Leu Pro Leu Glu Ser Ser Thr Ile Thr Ser Pro Thr Glu Ser Gly Ser
            900                 905                 910

Ser Asp Thr Glu Glu Thr Pro Ser Ile Ser Glu Gly Pro Lys Gly Asn
        915                 920                 925

Glu Gln Lys Lys Arg Asp Asp Asp Ser Leu Ser Lys Ile Ser Val Ser
    930                 935                 940

Pro Glu Asn Ser Arg Pro Glu Thr Asp Ala Lys Asp Thr Ser Asn Leu
945                 950                 955                 960

Leu Lys Leu Lys Gly Asp Val Asp Ile Ser Met Pro Lys Ala Val Ile
                965                 970                 975

Gly Ser Ser Pro Asn Asp Asn Ile Asn Val Thr Glu Gln Gly Asp Asn
            980                 985                 990

Ile Ser Gly Val Asn Ser Lys Pro  Leu Ser Asp Asp Val  Arg Pro Asp
        995                 1000                1005

Lys Asn  His Glu Glu Val Lys  Glu His Thr Ser Asn  Ser Asp Asn
    1010                1015                1020

Val Gln  Gln Ser Gly Gly Ile  Val Asn Met Asn Val  Glu Lys Glu
    1025                1030                1035

Leu Lys  Asp Thr Leu Glu Asn  Pro Ser Ser Ser Leu  Asp Glu Gly
    1040                1045                1050
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Lys Ala  His Glu Glu Leu Ser  Glu Pro Asn Leu Ser  Ser Asp Gln
    1055                1060                1065

Asp Met  Ser Asn Thr Pro Gly  Pro Leu Asp Asn Thr  Ser Glu Glu
    1070                1075                1080

Thr Thr  Glu Arg Ile Ser Asn  Asn Glu Tyr Lys Val  Asn Glu Arg
    1085                1090                1095

Glu Gly  Glu Arg Thr Leu Thr  Lys Glu Tyr Glu Asp  Ile Val Leu
    1100                1105                1110

Lys Ser  His Met Asn Arg Glu  Ser Asp Asp Gly Glu  Leu Tyr Asp
    1115                1120                1125

Glu Asn  Ser Asp Leu Ser Thr  Val Asn Asp Glu Ser  Glu Asp Ala
    1130                1135                1140

Glu Ala  Lys Met Lys Gly Asn  Asp Thr Ser Glu Met  Ser His Asn
    1145                1150                1155

Ser Ser  Gln His Ile Glu Ser  Asp Gln Gln Lys Asn  Asp Met Lys
    1160                1165                1170

Thr Val  Gly Asp Leu Gly Thr  Thr His Val Gln Asn  Glu Ile Ser
    1175                1180                1185

Val Pro  Val Thr Gly Glu Ile  Asp Glu Lys Leu Arg  Glu Ser Lys
    1190                1195                1200

Glu Ser  Lys Ile His Lys Ala  Glu Glu Glu Arg Leu  Ser His Thr
    1205                1210                1215

Asp Ile  His Lys Ile Asn Pro  Glu Asp Arg Asn Ser  Asn Thr Leu
    1220                1225                1230

His Leu  Lys Asp Ile Arg Asn  Glu Glu Asn Glu Arg  His Leu Thr
    1235                1240                1245

Asn Gln  Asn Ile Asn Ile Ser  Gln Glu Arg Asp Leu  Gln Lys His
    1250                1255                1260

Gly Phe  His Thr Met Asn Asn  Leu His Gly Asp Gly  Val Ser Glu
    1265                1270                1275

Arg Ser  Gln Ile Asn His Ser  His His Gly Asn Arg  Gln Asp Arg
    1280                1285                1290

Gly Gly  Asn Ser Gly Asn Val  Leu Asn Met Arg Ser  Asn Asn Asn
    1295                1300                1305

Asn Phe  Asn Asn Ile Pro Ser  Arg Tyr Asn Leu Tyr  Asp Lys Lys
    1310                1315                1320

Leu Asp  Leu Asp Leu Tyr Glu  Asn Arg Asn Asp Ser  Thr Thr Lys
    1325                1330                1335

Glu Leu  Ile Lys Lys Leu Ala  Glu Ile Asn Lys Cys  Glu Asn Glu
    1340                1345                1350

Ile Ser  Val Lys Tyr Cys Asp  His Met Ile His Glu  Glu Ile Pro
    1355                1360                1365

Leu Lys  Thr Cys Thr Lys Glu  Lys Thr Arg Asn Leu  Cys Cys Ala
    1370                1375                1380

Val Ser  Asp Tyr Cys Met Ser  Tyr Phe Thr Tyr Asp  Ser Glu Glu
    1385                1390                1395

Tyr Tyr  Asn Cys Thr Lys Arg  Glu Phe Asp Asp Pro  Ser Tyr Thr
    1400                1405                1410

Cys Phe  Arg Lys Glu Ala Phe  Ser Ser Met Pro Tyr  Tyr Ala Gly
    1415                1420                1425

Ala Gly  Val Leu Phe Ile Ile  Leu Val Ile Leu Gly  Ala Ser Gln
    1430                1435                1440
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Ala Lys  Tyr Gln Ser Ser Glu  Gly Val Met Asn Glu  Asn Asn Glu
    1445                1450                1455

Asn Asn  Phe Leu Phe Glu Val  Thr Asp Asn Leu Asp  Lys Leu Ser
    1460                1465                1470

Asn Met  Phe Asn Gln Gln Val  Gln Glu Thr Asn Ile  Asn Asp Phe
    1475                1480                1485

Ser Glu  Tyr His Glu Asp Ile  Asn Asp Ile Asn Phe  Lys Lys
    1490                1495                1500


<210> SEQ ID NO 14
<211> LENGTH: 4509
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 14

atgaaatgta atattagtat atatttttt gcttccttct ttgtgttata ttttgcaaaa     60

gctaggaatg aatatgatat aaaagagaat gaaaaatttt tagacgtgta taaagaaaaa    120

tttaatgaat tagataaaaa gaaatatgga aatgttcaaa aaactgataa gaaaatattt    180

acttttatag aaaataaatt agatatttta aataattcaa aatttaataa aagatggaag    240

agttatggaa ctccagataa tatagataaa aatatgtctt taataaataa acataataat    300

gaagaaatgt ttaacaacaa ttatcaatca tttttatcga caagttcatt aataaagcaa    360

aataaatatg ttcctattaa cgctgtacgt gtgtctagga tattaagttt cctggattct    420

agaattaata atggaagaaa tacttcatct aataacgaag ttttaagtaa ttgtagggaa    480

aaaaggaaag gaatgaaatg ggattgtaaa aagaaaaatg atagaagcaa ctatgtatgt    540

attcctgatc gtagaatcca attatgcatt gttaatctta gcattattaa aacatataca    600

aaagagacca tgaaggatca tttcattgaa gcctctaaaa aagaatctca acttttgctt    660

aaaaaaaatg ataacaaata taattctaaa ttttgtaatg atttgaagaa tagtttttta    720

gattatggac atcttgctat gggaaatgat atggattttg gaggttattc aactaaggca    780

gaaaacaaaa ttcaagaagt ttttaaaggg gctcatgggg aaataagtga acataaaatt    840

aaaaatttta gaaaaaaatg gtggaatgaa tttagagaga aactttggga agctatgtta    900

tctgagcata aaaataatat aaataattgt aaaaatattc cccaagaaga attacaaatt    960

actcaatgga taaaagaatg gcatggagaa tttttgcttg aaagagataa tagatcaaaa   1020

ttgccaaaaa gtaaatgtaa aaataataca ttatatgaag catgtgagaa ggaatgtatt   1080

gatccatgta tgaaatatag agattggatt attagaagta aatttgaatg gcatacgtta   1140

tcgaaagaat atgaaactca aaaagttcca aaggaaaatg cggaaaatta tttaatcaaa   1200

atttcagaaa acaagaatga tgctaaagta agtttattat tgaataattg tgatgctgaa   1260

tattcaaaat attgtgattg taaacatact actactctcg ttaaaagcgt tttaaatggt   1320

aacgacaata caattaagga aaagcgtgaa catattgatt tagatgattt ttctaaattt   1380

ggatgtgata aaaattccgt tgatacaaac acaaaggtgt gggaatgtaa aaaaccttat   1440

aaattatcca ctaaagatgt atgtgtacct ccgaggaggc aagaattatg tcttggaaac   1500

attgatagaa tatacgataa aaacctatta atgataaaag agcatattct tgctattgca   1560

atatatgaat caagaatatt gaaacgaaaa tataagaata aagatgataa agaagtttgt   1620

aaaatcataa ataaaacttt cgctgatata agagatatta taggaggtac tgattattgg   1680

aatgatttga gcaatagaaa attagtagga aaaattaaca caaattcaaa ttatgttcac   1740

aggaataaac aaaatgataa gctttttcgt gatgagtggt ggaaagttat taaaaaagat   1800
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gtatggaatg tgatatcatg ggtattcaag gataaaactg tttgtaaaga agatgatatt 1860

gaaaatatac cacaattctt cagatggttt agtgaatggg gtgatgatta ttgccaggat 1920

aaaacaaaaa tgatagagac tctgaaggtt gaatgcaaag aaaaaccttg tgaagatgac 1980

aattgtaaac gtaaatgtaa ttcatataaa gaatggatat caaaaaaaaa agaagagtat 2040

aataaacaag ccaaacaata ccaagaatat caaaaaggaa ataattacaa aatgtattct 2100

gaatttaaat ctataaaacc agaagtttat ttaaagaaat actcggaaaa atgttctaac 2160

ctaaatttcg aagatgaatt taaggaagaa ttacattcag attataaaaa taaatgtacg 2220

atgtgtccag aagtaaagga tgtaccaatt tctataataa gaaataatga acaaacttcg 2280

caagaagcag ttcctgagga aagcactgaa atagcacaca gaacggaaac tcgtacggat 2340

gaacgaaaaa atcaggaacc agcaaataag gatttaaaga atccacaaca aagtgtagga 2400

gagaacggaa ctaaagattt attacaagaa gatttaggag gatcacgaag tgaagacgaa 2460

gtgacacaag aatttggagt aaatcatgga atacctaagg gtgaggatca aacgttagga 2520

aaatctgacg ccattccaaa cataggcgaa cccgaaacgg gaatttccac tacagaagaa 2580

agtagacatg aagaaggcca caataaacaa gcattgtcta cttcagtcga tgagcctgaa 2640

ttatctgata cacttcaatt gcatgaagat actaaagaaa atgataaact acccctagaa 2700

tcatctacaa tcacatctcc tacggaaagt ggaagttctg atacagagga aactccatct 2760

atctctgaag gaccaaaagg aaatgaacaa aaaaaacgtg atgacgatag tttgagtaaa 2820

ataagtgtat caccagaaaa ttcaagacct gaaactgatg ctaaagatac ttctaacttg 2880

ttaaaattaa aaggagatgt tgatattagt atgcctaaag cagttattgg gagcagtcct 2940

aatgataata taaatgttac tgaacaaggg gataatattt ccggggtgaa ttctaaacct 3000

ttatctgatg atgtacgtcc agataaaaat catgaagagg tgaaagaaca tactagtaat 3060

tctgataatg ttcaacagtc tggaggaatt gttaatatga atgttgagaa agaactaaaa 3120

gatactttag aaaatccttc tagtagcttg gatgaaggaa aagcacatga agaattatca 3180

gaaccaaatc taagcagtga ccaagatatg tctaatacac ctggaccttt ggataacacc 3240

agtgaagaaa ctacagaaag aattagtaat aatgaatata aagttaacga gagggaaggt 3300

gagagaacgc ttactaagga atatgaagat attgttttga aaagtcatat gaatagagaa 3360

tcagacgatg gtgaattata tgacgaaaat tcagacttat ctactgtaaa tgatgaatca 3420

gaagacgctg aagcaaaaat gaaaggaaat gatacatctg aaatgtcgca taatagtagt 3480

caacatattg agagtgatca acagaaaaac gatatgaaaa ctgttggtga tttgggaacc 3540

acacatgtac aaaacgaaat tagtgttcct gttacaggag aaattgatga aaaattaagg 3600

gaaagtaaag aatcaaaaat tcataaggct gaagaggaaa gattaagtca tacagatata 3660

cataaaatta atcctgaaga tagaaatagt aatacattac atttaaaaga tataagaaat 3720

gaggaaaacg aaagacactt aactaatcaa aacattaata ttagtcaaga aagggatttg 3780

caaaaacatg gattccatac catgaataat ctacatggag atggagtttc cgaaagaagt 3840

caaattaatc atagtcatca tggaaacaga caagatcggg ggggaaattc tgggaatgtt 3900

ttaaatatga gatctaataa taataatttt aataatattc caagtagata taatttatat 3960

gataaaaaat tagatttaga tctttatgaa aacagaaatg atagtacaac aaaagaatta 4020

ataaagaaat tagcagaaat aaataaatgt gagaacgaaa tttctgtaaa atattgtgac 4080

catatgattc atgaagaaat cccattaaaa acatgcacta aagaaaaaac aagaaatctg 4140

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tgttgtgcag tatcagatta ctgtatgagc tattttacat atgattcaga ggaatattat   4200

aattgtacga aaagggaatt tgatgatcca tcttatacat gtttcagaaa ggaggctttt   4260

tcaagtatgc catattatgc aggagcaggt gtgttattta ttatattggt tattttaggt   4320

gcttcacaag ccaaatatca aagttctgaa ggagttatga atgagaataa tgagaataat   4380

tttttatttg aagttactga taatttagat aaattatcca atatgttcaa tcaacaagta   4440

caggaaacta atatcaacga tttttctgaa taccatgagg atataaatga tattaatttt   4500

aagaaatga                                                           4509
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<210> SEQ ID NO 15
<211> LENGTH: 2747
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 15

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Met Asp Ser Thr Ser Thr Ile Ala Asn Lys Ile Glu Glu Tyr Leu Gly
1               5                   10                  15

Ala Lys Ser Asp Asp Ser Lys Ile Asp Glu Leu Leu Lys Ala Asp Pro
            20                  25                  30

Ser Glu Val Glu Tyr Tyr Arg Ser Gly Gly Asp Gly Asp Tyr Leu Lys
        35                  40                  45

Asn Asn Ile Cys Lys Ile Thr Val Asn His Ser Asp Ser Gly Lys Tyr
    50                  55                  60

Asp Pro Cys Glu Lys Lys Leu Pro Pro Tyr Asp Asp Asn Asp Gln Trp
65                  70                  75                  80

Lys Cys Gln Gln Asn Ser Ser Asp Gly Ser Gly Lys Pro Glu Asn Ile
                85                  90                  95

Cys Val Pro Pro Arg Arg Glu Arg Leu Cys Thr Tyr Asn Leu Glu Asn
            100                 105                 110

Leu Lys Phe Asp Lys Ile Arg Asp Asn Asn Ala Phe Leu Ala Asp Val
        115                 120                 125

Leu Leu Thr Ala Arg Asn Glu Gly Glu Lys Ile Val Gln Asn His Pro
    130                 135                 140

Asp Thr Asn Ser Ser Asn Val Cys Asn Ala Leu Glu Arg Ser Phe Ala
145                 150                 155                 160

Asp Leu Ala Asp Ile Ile Arg Gly Thr Asp Gln Trp Lys Gly Thr Asn
                165                 170                 175

Ser Asn Leu Glu Lys Asn Leu Lys Gln Met Phe Ala Lys Ile Arg Glu
            180                 185                 190

Asn Asp Lys Val Leu Gln Asp Lys Tyr Pro Lys Asp Gln Lys Tyr Thr
        195                 200                 205

Lys Leu Arg Glu Ala Trp Trp Asn Ala Asn Arg Gln Lys Val Trp Glu
    210                 215                 220

Val Ile Thr Cys Gly Ala Arg Ser Asn Asp Leu Leu Ile Lys Arg Gly
225                 230                 235                 240

Trp Arg Thr Ser Gly Lys Ser Asp Arg Lys Lys Asn Phe Glu Leu Cys
                245                 250                 255

Arg Lys Cys Gly His Tyr Glu Lys Glu Val Pro Thr Lys Leu Asp Tyr
            260                 265                 270

Val Pro Gln Phe Leu Arg Trp Leu Thr Glu Trp Ile Glu Asp Phe Tyr
        275                 280                 285

Arg Glu Lys Gln Asn Leu Ile Asp Asp Met Glu Arg His Arg Glu Glu
    290                 295                 300
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Cys Thr Arg Glu Asp His Lys Ser Lys Glu Gly Thr Ser Tyr Cys Ser
305                 310                 315                 320

Thr Cys Lys Asp Lys Cys Lys Lys Tyr Cys Glu Cys Val Lys Lys Trp
                325                 330                 335

Lys Thr Glu Trp Glu Asn Gln Glu Asn Lys Tyr Lys Asp Leu Tyr Glu
            340                 345                 350

Gln Asn Lys Asn Lys Thr Ser Gln Lys Asn Thr Ser Arg Tyr Asp Asp
        355                 360                 365

Tyr Val Lys Asp Phe Phe Glu Lys Leu Glu Ala Asn Tyr Ser Ser Leu
    370                 375                 380

Glu Asn Tyr Ile Lys Gly Asp Pro Tyr Phe Ala Glu Tyr Ala Thr Lys
385                 390                 395                 400

Leu Ser Phe Ile Leu Asn Pro Ser Asp Ala Asn Asn Pro Ser Gly Glu
                405                 410                 415

Thr Ala Asn His Asn Asp Glu Ala Cys Asn Cys Asn Glu Ser Gly Ile
            420                 425                 430

Ser Ser Val Gly Gln Ala Gln Thr Ser Gly Pro Ser Ser Asn Lys Thr
        435                 440                 445

Cys Ile Thr His Ser Ser Ile Lys Thr Asn Lys Lys Lys Glu Cys Lys
    450                 455                 460

Asp Val Lys Leu Gly Val Arg Glu Asn Asp Lys Asp Leu Lys Ile Cys
465                 470                 475                 480

Val Ile Glu Asp Thr Ser Leu Ser Gly Val Asp Asn Cys Cys Cys Gln
                485                 490                 495

Asp Leu Leu Gly Ile Leu Gln Glu Asn Cys Ser Asp Asn Lys Arg Gly
            500                 505                 510

Ser Ser Ser Asn Asp Ser Cys Asp Asn Lys Asn Gln Asp Glu Cys Gln
        515                 520                 525

Lys Lys Leu Glu Lys Val Phe Ala Ser Leu Thr Asn Gly Tyr Lys Cys
    530                 535                 540

Asp Lys Cys Lys Ser Gly Thr Ser Arg Ser Lys Lys Lys Trp Ile Trp
545                 550                 555                 560

Lys Lys Ser Ser Gly Asn Glu Glu Gly Leu Gln Glu Glu Tyr Ala Asn
                565                 570                 575

Thr Ile Gly Leu Pro Pro Arg Thr Gln Ser Leu Tyr Leu Gly Asn Leu
            580                 585                 590

Pro Lys Leu Glu Asn Val Cys Glu Asp Val Lys Asp Ile Asn Phe Asp
        595                 600                 605

Thr Lys Glu Lys Phe Leu Ala Gly Cys Leu Ile Val Ser Phe His Glu
    610                 615                 620

Gly Lys Asn Leu Lys Lys Arg Tyr Pro Gln Asn Lys Asn Ser Gly Asn
625                 630                 635                 640

Lys Glu Asn Leu Cys Lys Ala Leu Glu Tyr Ser Phe Ala Asp Tyr Gly
                645                 650                 655

Asp Leu Ile Lys Gly Thr Ser Ile Trp Asp Asn Glu Tyr Thr Lys Asp
            660                 665                 670

Leu Glu Leu Asn Leu Gln Asn Asn Phe Gly Lys Leu Phe Gly Lys Tyr
        675                 680                 685

Ile Lys Lys Asn Asn Thr Ala Glu Gln Asp Thr Ser Tyr Ser Ser Leu
    690                 695                 700

Asp Glu Leu Arg Glu Ser Trp Trp Asn Thr Asn Lys Lys Tyr Ile Trp
705                 710                 715                 720

Thr Ala Met Lys His Gly Ala Glu Met Asn Ile Thr Thr Cys Asn Ala
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               725                 730                 735

Asp Gly Ser Val Thr Gly Ser Gly Ser Ser Cys Asp Asp Ile Pro Thr
            740                 745                 750

Ile Asp Leu Ile Pro Gln Tyr Leu Arg Phe Leu Gln Glu Trp Val Glu
        755                 760                 765

Asn Phe Cys Glu Gln Arg Gln Ala Lys Val Lys Asp Val Ile Thr Asn
    770                 775                 780

Cys Lys Ser Cys Lys Glu Ser Gly Asn Lys Cys Lys Thr Glu Cys Lys
785                 790                 795                 800

Thr Lys Cys Lys Asp Glu Cys Glu Lys Tyr Lys Lys Phe Ile Glu Ala
                805                 810                 815

Cys Gly Thr Ala Gly Gly Gly Ile Gly Thr Ala Gly Ser Pro Trp Ser
            820                 825                 830

Lys Arg Trp Asp Gln Ile Tyr Lys Arg Tyr Ser Lys His Ile Glu Asp
        835                 840                 845

Ala Lys Arg Asn Arg Lys Ala Gly Thr Lys Asn Cys Gly Thr Ser Ser
    850                 855                 860

Thr Thr Asn Ala Ala Ala Ser Thr Asp Glu Asn Lys Cys Val Gln Ser
865                 870                 875                 880

Asp Ile Asp Ser Phe Phe Lys His Leu Ile Asp Ile Gly Leu Thr Thr
                885                 890                 895

Pro Ser Ser Tyr Leu Ser Asn Val Leu Asp Asp Asn Ile Cys Gly Ala
            900                 905                 910

Asp Lys Ala Pro Trp Thr Thr Tyr Thr Thr Tyr Thr Thr Thr Glu Lys
        915                 920                 925

Cys Asn Lys Glu Arg Asp Lys Ser Lys Ser Gln Ser Ser Asp Thr Leu
    930                 935                 940

Val Val Val Asn Val Pro Ser Pro Leu Gly Asn Thr Pro Tyr Arg Tyr
945                 950                 955                 960

Lys Tyr Ala Cys Gln Cys Lys Ile Pro Thr Asn Glu Glu Thr Cys Asp
                965                 970                 975

Asp Arg Lys Glu Tyr Met Asn Gln Trp Ser Cys Gly Ser Ala Arg Thr
            980                 985                 990

Met Lys Arg Gly Tyr Lys Asn Asp  Asn Tyr Glu Leu Cys  Lys Tyr Asn
        995                 1000                1005

Gly Val  Asp Val Lys Pro Thr  Thr Val Arg Ser Asn  Ser Ser Lys
    1010                1015                1020

Leu Asp  Gly Asn Asp Val Thr  Phe Phe Asn Leu Phe  Glu Gln Trp
    1025                1030                1035

Asn Lys  Glu Ile Gln Tyr Gln  Ile Glu Gln Tyr Met  Thr Asn Ala
    1040                1045                1050

Asn Ile  Ser Cys Ile Asp Glu  Lys Glu Val Leu Asp  Ser Val Ser
    1055                1060                1065

Asp Glu  Gly Thr Pro Lys Val  Arg Gly Gly Tyr Glu  Asp Gly Arg
    1070                1075                1080

Asn Asn  Asn Thr Asp Gln Gly  Thr Asn Cys Lys Glu  Lys Cys Lys
    1085                1090                1095

Cys Tyr  Lys Leu Trp Ile Glu  Lys Ile Asn Asp Gln  Trp Gly Lys
    1100                1105                1110

Gln Lys  Asp Asn Tyr Asn Lys  Phe Arg Ser Lys Gln  Ile Tyr Asp
    1115                1120                1125

Ala Asn  Lys Gly Ser Gln Asn  Lys Lys Val Val Ser  Leu Ser Asn
    1130                1135                1140
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Phe Leu  Phe Phe Ser Cys Trp  Glu Glu Tyr Ile Gln  Lys Tyr Phe
    1145                1150                1155

Asn Gly  Asp Trp Ser Lys Ile  Lys Asn Ile Gly Ser  Asp Thr Phe
    1160                1165                1170

Glu Phe  Leu Ile Lys Lys Cys  Gly Asn Asn Ser Ala  His Gly Glu
    1175                1180                1185

Glu Ile  Phe Ser Glu Lys Leu  Lys Asn Ala Glu Lys  Lys Cys Lys
    1190                1195                1200

Glu Asn  Glu Ser Thr Asp Thr  Asn Ile Asn Lys Ser  Glu Thr Ser
    1205                1210                1215

Cys Asp  Leu Asn Ala Thr Asn  Tyr Ile Arg Gly Cys  Gln Ser Lys
    1220                1225                1230

Thr Tyr  Asp Gly Lys Ile Phe  Pro Gly Lys Gly Gly  Glu Lys Gln
    1235                1240                1245

Trp Ile  Cys Lys Asp Thr Ile  Ile His Gly Asp Thr  Asn Gly Ala
    1250                1255                1260

Cys Ile  Pro Pro Arg Thr Gln  Asn Leu Cys Val Gly  Glu Leu Trp
    1265                1270                1275

Asp Lys  Ser Tyr Gly Gly Arg  Ser Asn Ile Lys Asn  Asp Thr Lys
    1280                1285                1290

Glu Leu  Leu Lys Glu Lys Ile  Lys Asn Ala Ile His  Lys Glu Thr
    1295                1300                1305

Glu Leu  Leu Tyr Glu Tyr His  Asp Thr Gly Thr Ala  Ile Ile Ser
    1310                1315                1320

Lys Asn  Asp Lys Lys Gly Gln  Lys Gly Lys Asn Asp  Pro Asn Gly
    1325                1330                1335

Leu Pro  Lys Gly Phe Cys His  Ala Val Gln Arg Ser  Phe Ile Asp
    1340                1345                1350

Tyr Lys  Asn Met Ile Leu Gly  Thr Ser Val Asn Ile  Tyr Glu His
    1355                1360                1365

Ile Gly  Lys Leu Gln Glu Asp  Ile Lys Lys Ile Ile  Glu Lys Gly
    1370                1375                1380

Thr Pro  Gln Gln Lys Asp Lys  Ile Gly Gly Val Gly  Ser Ser Thr
    1385                1390                1395

Glu Asn  Val Asn Ala Trp Trp  Lys Gly Ile Glu Arg  Glu Met Trp
    1400                1405                1410

Asp Ala  Val Arg Cys Ala Ile  Thr Lys Ile Asn Lys  Lys Asn Asn
    1415                1420                1425

Asn Ser  Ile Phe Asn Gly Asp  Glu Cys Gly Val Ser  Pro Pro Thr
    1430                1435                1440

Gly Asn  Asp Glu Asp Gln Ser  Val Ser Trp Phe Lys  Glu Trp Gly
    1445                1450                1455

Glu Gln  Phe Cys Ile Glu Arg  Leu Arg Tyr Glu Gln  Asn Ile Arg
    1460                1465                1470

Glu Ala  Cys Thr Ile Asn Gly  Lys Asn Glu Lys Lys  Cys Ile Asn
    1475                1480                1485

Ser Lys  Ser Gly Gln Gly Asp  Lys Ile Gln Gly Ala  Cys Lys Arg
    1490                1495                1500

Lys Cys  Glu Lys Tyr Lys Lys  Tyr Ile Ser Glu Lys  Lys Gln Glu
    1505                1510                1515

Trp Asp  Lys Gln Lys Thr Lys  Tyr Glu Asn Lys Tyr  Val Gly Lys
    1520                1525                1530
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Ser Ala  Ser Asp Leu Leu Lys  Glu Asn Tyr Pro Glu  Cys Ile Ser
    1535                1540                1545

Ala Asn  Phe Asp Phe Ile Phe  Asn Asp Asn Ile Glu  Tyr Lys Thr
    1550                1555                1560

Tyr Tyr  Pro Tyr Gly Asp Tyr  Ser Ser Ile Cys Ser  Cys Glu Gln
    1565                1570                1575

Val Lys  Tyr Tyr Lys Tyr Asn  Asn Ala Glu Lys Lys  Asn Asn Lys
    1580                1585                1590

Ser Leu  Cys Tyr Glu Lys Asp  Asn Asp Met Thr Trp  Ser Lys Lys
    1595                1600                1605

Tyr Ile  Lys Lys Leu Glu Asn  Gly Arg Ser Leu Glu  Gly Val Tyr
    1610                1615                1620

Val Pro  Pro Arg Arg Gln Gln  Leu Cys Leu Tyr Glu  Leu Phe Pro
    1625                1630                1635

Ile Ile  Ile Lys Asn Glu Glu  Gly Met Glu Lys Ala  Lys Glu Glu
    1640                1645                1650

Leu Leu  Glu Thr Leu Gln Ile  Val Ala Glu Arg Glu  Ala Tyr Tyr
    1655                1660                1665

Leu Trp  Lys Gln Tyr Asn Pro  Thr Gly Lys Gly Ile  Asp Asp Ala
    1670                1675                1680

Asn Lys  Lys Ala Cys Cys Ala  Ile Arg Gly Ser Phe  Tyr Asp Leu
    1685                1690                1695

Glu Asp  Ile Ile Lys Gly Asn  Asp Leu Val His Asp  Glu Tyr Thr
    1700                1705                1710

Lys Tyr  Ile Asp Ser Lys Leu  Asn Glu Ile Phe Gly  Ser Ser Asn
    1715                1720                1725

Thr Asn  Asp Ile Asp Thr Lys  Arg Ala Arg Thr Asp  Trp Trp Glu
    1730                1735                1740

Asn Glu  Thr Ile Thr Asn Gly  Thr Asp Arg Lys Thr  Ile Arg Gln
    1745                1750                1755

Leu Val  Trp Asp Ala Met Gln  Ser Gly Val Arg Tyr  Ala Val Glu
    1760                1765                1770

Glu Lys  Asn Glu Asn Phe Pro  Leu Cys Met Gly Val  Glu His Ile
    1775                1780                1785

Gly Ile  Ala Lys Pro Gln Phe  Ile Arg Trp Leu Glu  Glu Trp Thr
    1790                1795                1800

Asn Glu  Phe Cys Glu Lys Tyr  Thr Lys Tyr Phe Glu  Asp Met Lys
    1805                1810                1815

Ser Lys  Cys Asp Pro Pro Lys  Arg Ala Asp Thr Cys  Gly Asp Asn
    1820                1825                1830

Ser Asn  Ile Glu Cys Lys Lys  Ala Cys Ala Asn Tyr  Thr Asn Trp
    1835                1840                1845

Leu Asn  Pro Lys Arg Ile Glu  Trp Asn Gly Met Ser  Asn Tyr Tyr
    1850                1855                1860

Asn Lys  Ile Tyr Arg Lys Ser  Asn Lys Glu Ser Glu  Asp Gly Lys
    1865                1870                1875

Asp Tyr  Ser Met Ile Met Ala  Pro Thr Val Ile Asp  Tyr Leu Asn
    1880                1885                1890

Lys Arg  Cys His Gly Glu Ile  Asn Gly Asn Tyr Ile  Cys Cys Ser
    1895                1900                1905

Cys Lys  Asn Ile Gly Ala Tyr  Asn Thr Thr Ser Gly  Thr Val Asn
    1910                1915                1920

Lys Lys  Leu Gln Lys Lys Glu  Thr Glu Cys Glu Glu  Glu Lys Gly
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    1925                1930                1935

Pro Leu  Asp Leu Met Asn Glu  Val Leu Asn Lys Met  Asp Lys Lys
    1940                1945                1950

Tyr Ser  Ala His Lys Met Lys  Cys Thr Glu Val Tyr  Leu Glu His
    1955                1960                1965

Val Glu  Glu Gln Leu Asn Glu  Ile Asp Asn Ala Ile  Lys Asp Tyr
    1970                1975                1980

Lys Leu  Tyr Pro Leu Asp Arg  Cys Phe Asp Asp Gln  Thr Lys Met
    1985                1990                1995

Lys Val  Cys Asp Leu Ile Ala  Asp Ala Ile Gly Cys  Lys Asp Lys
    2000                2005                2010

Thr Lys  Leu Asp Glu Leu Asp  Glu Trp Asn Asp Met  Asp Leu Arg
    2015                2020                2025

Gly Thr  Tyr Asn Lys His Lys  Gly Val Leu Ile Pro  Pro Arg Arg
    2030                2035                2040

Arg Gln  Leu Cys Phe Ser Arg  Ile Val Arg Gly Pro  Ala Asn Leu
    2045                2050                2055

Arg Ser  Leu Asn Glu Phe Lys  Glu Glu Ile Leu Lys  Gly Ala Gln
    2060                2065                2070

Ser Glu  Gly Lys Phe Leu Gly  Asn Tyr Tyr Lys Glu  His Lys Asp
    2075                2080                2085

Lys Glu  Lys Ala Leu Glu Ala  Met Lys Asn Ser Phe  Tyr Asp Tyr
    2090                2095                2100

Glu Asp  Ile Ile Lys Gly Thr  Asp Met Leu Thr Asn  Ile Glu Phe
    2105                2110                2115

Lys Asp  Ile Lys Ile Lys Leu  Asp Arg Leu Leu Glu  Lys Glu Thr
    2120                2125                2130

Asn Asn  Thr Lys Lys Ala Glu  Asp Trp Trp Lys Thr  Asn Lys Lys
    2135                2140                2145

Ser Ile  Trp Asn Ala Met Leu  Cys Gly Tyr Lys Lys  Ser Gly Asn
    2150                2155                2160

Lys Ile  Ile Asp Pro Ser Trp  Cys Thr Ile Pro Thr  Thr Glu Thr
    2165                2170                2175

Pro Pro  Gln Phe Leu Arg Trp  Ile Lys Glu Trp Gly  Thr Asn Val
    2180                2185                2190

Cys Ile  Gln Lys Gln Glu His  Lys Glu Tyr Val Lys  Ser Lys Cys
    2195                2200                2205

Ser Asn  Val Thr Asn Leu Gly  Ala Gln Ala Ser Glu  Ser Asn Asn
    2210                2215                2220

Cys Thr  Ser Glu Ile Lys Lys  Tyr Gln Glu Trp Ser  Arg Lys Arg
    2225                2230                2235

Ser Ile  Gln Trp Glu Thr Ile  Ser Lys Arg Tyr Lys  Lys Tyr Lys
    2240                2245                2250

Arg Met  Asp Ile Leu Lys Asp  Val Lys Glu Pro Asp  Ala Asn Thr
    2255                2260                2265

Tyr Leu  Arg Glu His Cys Ser  Lys Cys Pro Cys Gly  Phe Asn Asp
    2270                2275                2280

Met Glu  Glu Met Asn Asn Asn  Glu Asp Asn Glu Lys  Glu Ala Phe
    2285                2290                2295

Lys Gln  Ile Lys Glu Gln Val  Lys Ile Pro Ala Glu  Leu Glu Asp
    2300                2305                2310

Val Ile  Tyr Arg Ile Lys His  His Glu Tyr Asp Lys  Gly Asn Asp
    2315                2320                2325
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Tyr Ile  Cys Asn Lys Tyr Lys  Asn Ile His Asp Arg  Met Lys Lys
    2330                 2335                 2340

Asn Asn  Gly Asn Phe Val Thr  Asp Asn Phe Val Lys  Lys Ser Trp
    2345                 2350                 2355

Glu Ile  Ser Asn Gly Val Leu  Ile Pro Pro Arg Arg  Lys Asn Leu
    2360                 2365                 2370

Phe Leu  Tyr Ile Asp Pro Ser  Lys Ile Cys Glu Tyr  Lys Lys Asp
    2375                 2380                 2385

Pro Lys  Leu Phe Lys Asp Phe  Ile Tyr Trp Ser Ala  Phe Thr Glu
    2390                 2395                 2400

Val Glu  Arg Leu Lys Lys Ala  Tyr Gly Gly Ala Arg  Ala Lys Val
    2405                 2410                 2415

Val His  Ala Met Lys Tyr Ser  Phe Thr Asp Ile Gly  Ser Ile Ile
    2420                 2425                 2430

Lys Gly  Asp Asp Met Met Glu  Lys Asn Ser Ser Asp  Lys Ile Gly
    2435                 2440                 2445

Lys Ile  Leu Gly Asp Thr Asp  Gly Gln Asn Glu Lys  Arg Lys Lys
    2450                 2455                 2460

Trp Trp  Asp Met Asn Lys Tyr  His Ile Trp Glu Ser  Met Leu Cys
    2465                 2470                 2475

Gly Tyr  Arg Glu Ala Glu Gly  Asp Thr Glu Thr Asn  Glu Asn Cys
    2480                 2485                 2490

Arg Phe  Pro Asp Ile Glu Ser  Val Pro Gln Phe Leu  Arg Trp Phe
    2495                 2500                 2505

Gln Glu  Trp Ser Glu Asn Phe  Cys Asp Arg Arg Gln  Lys Leu Tyr
    2510                 2515                 2520

Asp Lys  Leu Asn Ser Glu Cys  Ile Ser Ala Glu Cys  Thr Asn Gly
    2525                 2530                 2535

Ser Val  Asp Asn Ser Lys Cys  Thr His Ala Cys Val  Asn Tyr Lys
    2540                 2545                 2550

Asn Tyr  Ile Leu Thr Lys Lys  Thr Glu Tyr Glu Ile  Gln Thr Asn
    2555                 2560                 2565

Lys Tyr  Asp Asn Glu Phe Lys  Asn Lys Asn Ser Asn  Asp Lys Asp
    2570                 2575                 2580

Ala Pro  Asp Tyr Leu Lys Glu  Lys Cys Asn Asp Asn  Lys Cys Glu
    2585                 2590                 2595

Cys Leu  Asn Lys His Ile Asp  Asp Lys Asn Lys Thr  Trp Lys Asn
    2600                 2605                 2610

Pro Tyr  Glu Thr Leu Glu Asp  Thr Phe Lys Ser Lys  Cys Asp Cys
    2615                 2620                 2625

Pro Lys  Pro Leu Pro Ser Pro  Ile Lys Pro Asp Asp  Leu Pro Pro
    2630                 2635                 2640

Gln Ala  Asp Glu Pro Phe Asp  Pro Thr Ile Leu Gln  Thr Thr Ile
    2645                 2650                 2655

Pro Phe  Gly Ile Ala Leu Ala  Leu Gly Ser Ile Ala  Phe Leu Phe
    2660                 2665                 2670

Met Lys  Val Ile Tyr Ile Tyr  Ile Tyr Ile Cys Val  Val Tyr Val
    2675                 2680                 2685

Cys Met  Tyr Val Cys Met Tyr  Val Cys Met Tyr Val  Cys Met Tyr
    2690                 2695                 2700

Val Cys  Met Tyr Val Cys Met  Tyr Val Cys Tyr Val  Tyr Met Leu
    2705                 2710                 2715
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Tyr Met  Tyr Leu Lys Tyr Val  Phe Ile Leu Lys Lys  Lys Lys Gly
    2720                2725                2730

Lys Ser  Asn Ile Gly Ile Tyr  Leu Leu Lys Lys Lys  Arg Glu
    2735                2740                2745


<210> SEQ ID NO 16
<211> LENGTH: 8244
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 16

atggatagta caagcactat tgctaacaaa attgaagaat atttaggtgc aaaatccgat     60

gattctaaaa tagacgaatt gttgaaagct gatcctagtg aagtggaata ctatagaagt    120

ggaggtgatg gagattactt aaaaaataat atttgtaaaa ttaccgtgaa tcattcagat    180

tctggaaagt atgatccttg tgaaaaaaaa ttacctcctt atgatgataa tgaccaatgg    240

aaatgtcagc aaaattcatc tgatggaagt ggaaaacctg aaaatatatg tgtccctccg    300

agaagagaaa gattatgtac gtataattta gaaaacttaa aatttgataa aattagggat    360

aataatgcat ttttggctga tgtattactt acagctagaa atgaaggaga aaaaatagtg    420

cagaatcatc cagatacaaa tagttccaat gtttgtaatg ctttagaaag aagttttgct    480

gatcttgcag atattattag aggtacagat caatggaaag gtactaatag taatttagaa    540

aaaaatttaa aacaaatgtt tgcaaaaata cgagaaaacg acaaggtact tcaagataaa    600

tacccaaagg accaaaaata tacaaaatta cgagaagctt ggtggaatgc taatagacaa    660

aaggtgtggg aagttattac ttgcggtgca cgaagtaacg atttactcat aaaacgtgga    720

tggagaacat ctggaaaatc tgatagaaaa aagaacttcg aattgtgccg caaatgtggc    780

cattatgaaa aagaggttcc taccaaatta gattatgtcc ctcaattctt aaggtggtta    840

acagaatgga tagaggattt ttatagagag aagcaaaatc tgatcgatga catggagagg    900

caccgtgaag agtgtacaag agaggatcat aaatctaaag aaggtacatc atattgtagt    960

acctgtaaag acaaatgtaa gaaatattgt gaatgtgtga agaaatggaa gaccgaatgg   1020

gaaaatcaag aaaataaata taaagattta tatgaacaaa acaaaaacaa aacttcgcaa   1080

aaaaatacat caagatatga tgattatgtt aaagattttt ttgaaaaact tgaagctaat   1140

tattcgtctc ttgaaaatta tataaagggt gatccttatt tcgcagaata tgcaaccaaa   1200

ttatcattta ttttaaatcc atcagatgct aataatccgt ctggagaaac agcaaaccat   1260

aatgatgaag catgtaactg taatgaatca ggaatttcat cagttggaca ggcacaaaca   1320

tcgggtccgt cgtcgaataa aacatgtatc acacatagct ctataaaaac taataagaaa   1380

aaagaatgta aagatgtaaa gttgggtgtt cgtgaaaatg ataaagattt gaaaatatgc   1440

gtaattgagg acacttcctt aagtggtgtt gataattgtt gttgccaaga tttattggga   1500

attcttcaag aaaattgtag tgataataaa cgtggatcta gttctaatga tagttgtgat   1560

aacaaaaatc aggatgaatg tcaaaagaaa ttagaaaaag tatttgcatc tttaacgaat   1620

ggttataaat gcgacaaatg taaatctgga acatcaagaa gtaaaaaaaa atggatatgg   1680

aaaaaatcct ctggtaatga agaaggatta caagaagaat atgctaacac cataggttta   1740

cccccaagaa cacaatcgtt atatttagga aatctaccta aacttgaaaa tgtgtgcgaa   1800

gatgtaaagg atattaattt tgatacaaaa gagaaatttc tagcaggatg cttaattgtt   1860

tcttttcatg aaggaaaaaa tttaaaaaaa agataccctc aaaataaaaa ttctggaaat   1920

aaagaaaatt tatgcaaagc tttagaatat agttttgctg attatggaga tttaattaaa   1980
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ggtacaagta tatgggataa tgaatataca aaagatctgg aactaaattt acaaaacaat 2040

tttggaaaac tttttggtaa atatataaaa aagaataata ctgctgaaca agatacttca 2100

tattcttctc ttgatgaatt aagagaatca tggtggaaca cgaacaaaaa atatatttgg 2160

acagcaatga aacatggtgc agaaatgaat attactacgt gtaatgctga tggtagtgtc 2220

actggtagtg gtagtagttg tgatgatatt cctacgattg atttgatccc gcaatattta 2280

cgtttttttgc aagaatgggt agaaaatttt tgcgaacaac gtcaagcaaa agtaaaagat 2340

gtgataacga actgtaagtc gtgtaaggaa agtggaaaca aatgtaaaac tgaatgtaaa 2400

acaaaatgta aagacgagtg tgaaaaatac aaaaaattta ttgaagcgtg tggtacagct 2460

ggtggtggta ttggtactgc tggatctcca tggagcaaaa ggtgggacca aatatataag 2520

aggtattcca aacatataga agacgcgaaa cgaaaccgta aagcgggcac aaaaaattgt 2580

ggtacaagta gtactacaaa tgctgccgca agtactgatg aaaataaatg tgtacaatca 2640

gatatcgatt cgtttttcaa acacttaatt gatataggat tgaccacacc gtcttcttat 2700

ttatcaaatg tacttgatga caacatatgt ggcgcggaca aagctccatg gacaacatac 2760

acgacataca cgacaacaga aaaatgtaat aaagaaagag ataaatcaaa gtcacaatca 2820

agtgatacgc ttgtggttgt aaatgttccg tctccactgg gcaacactcc ataccgatat 2880

aaatacgcat gccagtgtaa aataccaact aatgaagaaa catgtgatga tagaaaagaa 2940

tatatgaatc aatggagttg tggtagcgca cgaactatga aacgtggtta taaaaatgac 3000

aactacgaat tatgtaaata taatggtgta gatgtaaaac cgacaacagt tagatcaaat 3060

agctctaaat tagatggaaa tgatgtgacg ttctttaatt tgtttgaaca gtggaacaaa 3120

gaaatacaat atcagataga gcagtatatg acaaatgcga atatatcgtg cattgacgaa 3180

aaagaagtat tggatagtgt gtcagacgaa ggtactccta aagtacgtgg tggttatgaa 3240

gatggtagaa ataacaatac cgatcagggt acgaactgca aagaaaaatg taaatgttac 3300

aaattatgga tagaaaaaat taatgatcag tggggaaaac agaaagacaa ttataataaa 3360

tttcgaagta aacaaattta tgatgcaaat aaaggttctc agaataaaaa agttgttagt 3420

ttatctaatt ttttgttttt ttcatgttgg gaagaatata tacaaaaata tttcaatggc 3480

gattggagta aaattaagaa tataggatct gatacgtttg agtttttaat aaaaaaatgt 3540

ggaaacaatt cagctcatgg agaagaaata tttagtgaaa aattgaaaaa tgcagaaaaa 3600

aaatgtaagg aaaatgaaag tacagatacc aatattaata aaagtgaaac atcatgtgac 3660

cttaacgcaa ccaattatat tcgtgggtgt caatcaaaaa cttacgatgg aaaaatattt 3720

ccaggtaaag gaggcgagaa acaatggata tgtaaagata ctataataca tggagataca 3780

aatggtgcct gtatcccgcc aagaacacaa aatttatgtg ttggagagtt atgggataaa 3840

agttatggtg gaaggagtaa cattaaaaat gatacaaagg aattattaaa agagaaaata 3900

aaaaatgcta tacacaaaga aacagaatta ttgtatgaat accacgatac aggtacagca 3960

attatatcaa aaaatgataa aaaaggacaa aaaggaaaaa atgatcctaa tggattgcca 4020

aaaggttttt gtcatgctgt tcaaagaagt tttattgatt ataagaatat gattttgggt 4080

acaagtgtaa atatatatga acacattgga aaattacaag aagatataaa aaaaattatc 4140

gaaaaaggaa cacctcaaca aaaagacaaa ataggtggtg ttggtagtag tacagaaaac 4200

gtaaatgctt ggtggaaagg aattgaaagg gagatgtggg atgcagtaag atgtgctata 4260

acaaaaataa ataaaaaaaa taataatagt atatttaatg gtgatgagtg tggggtatcc 4320

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ccccaacag gaaatgatga ggatcagtcc gtttcgtggt ttaaagaatg gggcgaacag 4380

ttttgtatag aacgattacg atatgaacaa aatatacgtg aagcttgtac tattaatggt 4440

aagaatgaaa agaaatgtat taattcaaaa agtggtcaag gagataaaat acaaggagca 4500

tgtaaaagaa aatgtgaaaa atataaaaaa tatatttctg aaaaaaaaca agaatgggac 4560

aaacaaaaaa caaaatatga aaataaatat gtaggaaaat ctgcgagtga tttattgaaa 4620

gaaaattatc ctgaatgtat atcagcaaat tttgatttta tatttaacga taatattgaa 4680

tataagacat attatccata tggagattat agcagtatat gttcgtgcga acaagtaaaa 4740

tattacaaat ataataatgc tgagaaaaaa aataataaat cgctttgtta tgaaaaagat 4800

aatgatatga catggagtaa aaaatatata aaaaaattgg aaaatggtcg atcattagag 4860

ggagtatacg tccccccaag acggcaacaa ttatgtcttt atgaactatt tccaataatt 4920

ataaaaaacg aagaaggtat ggaaaaggca aaagaagaat tattggaaac attacaaata 4980

gttgcagaga gagaagcata ttatttatgg aaacagtata atccaactgg taaaggaatt 5040

gatgatgcga ataagaaagc ttgttgtgcc attcgtggaa gtttttatga tttggaagat 5100

attattaaag gcaacgattt agtgcatgac gaatacacga aatatataga cagtaaatta 5160

aacgaaattt tcggtagtag taatacaaat gatatagata caaaacgtgc gcgtacagat 5220

tggtgggaaa acgaaaccat tactaatgga actgatcgta aaacaattag gcagctagta 5280

tgggatgcta tgcaatctgg agtaagatat gcagtagaag agaaaaacga aaattttcct 5340

ctatgtatgg gagttgaaca tataggaata gccaaacctc aatttataag atggttggaa 5400

gaatggacaa atgagttttg tgagaaatat acaaaatatt tcgaagatat gaaatccaaa 5460

tgtgatcccc ccaaacgtgc tgatacttgt ggtgataata gtaatatcga atgtaaaaaa 5520

gcatgtgcaa attatacgaa ttggttaaat ccaaaaagga tagaatggaa tggaatgagc 5580

aattattata ataaaatata ccgtaaaagt aacaaagaat cggaagatgg aaaagattat 5640

tcaatgatta tggcacctac agtcattgac tatttgaaca aaagatgcca tggcgaaatt 5700

aatgggaact acatttgttg tagttgtaaa aatataggtg catataacac cacttcaggt 5760

acagttaata aaaaactaca aaaaaaggaa acagaatgtg aagaagaaaa aggacctcta 5820

gatttaatga acgaggtatt aaataaaatg gacaaaaaat atagcgcgca caagatgaag 5880

tgcacagaag tttacttgga acatgttgaa gaacaattaa acgaaattga caatgcaata 5940

aaagattaca agttatatcc tttagataga tgttttgatg atcagacaaa aatgaaggtg 6000

tgtgatttaa ttgcagatgc tataggatgt aaggataaaa caaaactgga tgaactggat 6060

gaatggaatg atatggacct gcgaggtact tataataagc ataaaggtgt tttaattcct 6120

cctagacgta gacaattatg tttctcaagg attgtgagag gtcccgcaaa tttaagaagc 6180

ttaaatgaat ttaaagaaga aattttaaaa ggagcccaat cggaaggtaa gtttttgggt 6240

aattattata aagaacataa agataaagaa aaggcgctag aagctatgaa aaacagtttt 6300

tacgattatg aagatataat aaaaggtact gatatgttaa caaatataga attcaaggat 6360

attaaaataa aactagacag attactagaa aaagagacta ataataccaa aaaagctgaa 6420

gattggtgga aaacaaataa gaaatctata tggaatgcta tgttatgtgg gtacaagaaa 6480

tctgggaata aaataataga tccatcatgg tgtaccatac ctactacaga aacccctccg 6540

caatttttac gatggataaa agaatgggga acaaatgtgt gtatacaaaa acaagagcat 6600

aaagaatacg ttaaatcaaa atgttctaat gttactaatt taggggcaca agcatcggaa 6660

tcaaataatt gtacatcaga aattaaaaaa tatcaagaat ggagcaggaa aaggtctatt 6720

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cagtgggaaa ctatatcgaa aagatataaa aaatataaac gtatggatat attaaaagat   6780

gtaaaggaac cagatgctaa tacatattta agggaacatt gttctaaatg tccgtgtgga   6840

tttaatgata tggaagaaat gaataacaat gaagacaacg aaaaagaagc atttaagcaa   6900

ataaaagaac aagttaagat tccagctgaa cttgaagacg ttatttaccg aataaaacat   6960

catgagtatg ataaaggtaa tgattatatt tgtaataaat ataaaaatat acacgatcgt   7020

atgaaaaaaa ataatggtaa ttttgtgact gataatttcg ttaaaaaatc ttgggaaatt   7080

agtaatggtg tgctaatacc tccacgaaga aaaaatttgt ttctgtacat tgatccatca   7140

aaaatatgtg aatataaaaa ggatcctaaa ttgtttaaag atttcattta ttggtcggca   7200

tttactgaag ttgaaaggtt aaaaaaagcg tatggtgggg ctagagcgaa agttgttcat   7260

gcaatgaaat atagttttac cgatatagga agtattatca aaggtgatga tatgatggaa   7320

aagaattcgt ctgataagat aggtaaaatt ttgggagata cagatggaca gaatgaaaaa   7380

cgtaaaaaat ggtgggacat gaataaatat cacatatggg aatccatgtt atgcggatat   7440

agagaagctg agggcgacac agaaacgaac gaaaattgca ggtttcctga tattgaatct   7500

gttccccaat ttctacgatg gtttcaagaa tggagcgaaa atttctgtga tagacgacaa   7560

aaattatatg ataaattgaa tagtgaatgt atatctgctg aatgcactaa tggatctgtt   7620

gataattcta aatgtactca tgcatgtgta aattataaaa attatatttt aacaaaaaaa   7680

acagaatatg aaattcaaac aaataaatat gataatgaat ttaaaaacaa aaatagtaat   7740

gataaagacg ccccagatta cttaaaagag aaatgtaatg ataataaatg tgaatgtctc   7800

aataaacata ttgatgataa aaacaaaaca tggaaaaatc cttatgaaac tctggaggac   7860

actttcaaaa gcaaatgtga ttgcccaaaa cctttaccat cccctataaa acctgatgac   7920

ttacccccc aagccgatga accgtttgac ccaactatac tacaaacaac cattccttt   7980

ggtattgcgt tggcgttagg gtcgatcgct ttccttttca tgaaggtaat atatatatat   8040

atatatatat gtgttgtata tgtatgtatg tatgtatgta tgtatgtatg tatgtatgta   8100

tgtatgtatg tatgtatgta tgtatgtatg tatgtatgtt atgtgtatat gttatatatg   8160

tatttaaaat atgtatttat attgaaaaag aaaaaaggaa aaagtaatat aggaatatat   8220

ctattaaaaa aaaaaagaga gtga                                         8244
```

<210> SEQ ID NO 17
<211> LENGTH: 362
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 17

```
Glu His Ile Cys Asp Phe Thr Lys Glu Lys Tyr Leu Leu Gly Lys Asn
1               5                   10                  15

Glu Lys Glu Tyr Cys Val Val Asn Ala Lys Pro Phe Asp Ser Val Thr
            20                  25                  30

Phe Ile Cys Pro Lys Lys Ile Gly Ala Gln Cys Phe Gln Asn Val Asn
        35                  40                  45

Thr Leu Asp Asp Ile Ser Ala Asp Lys Met Glu Ser Ser Lys Leu Ser
    50                  55                  60

Ile Asp Glu Leu Leu Tyr Gly Ser Thr Leu Tyr Gly Asp Thr Leu Leu
65                  70                  75                  80

Ile Ser Pro Thr Val Lys Gln Ser Thr Thr Phe Tyr Cys Phe Cys Asn
                85                  90                  95
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Leu Gln Met Glu Asp Leu Lys Lys Tyr Leu Lys Lys Arg Arg Leu Thr
            100                 105                 110

Lys Glu Lys Glu Asn Ala Lys Lys Lys Ser Thr Val Asn Val Asn Asp
        115                 120                 125

Leu Lys Asn Ala Asp Glu Asp Met Glu Val Val Val Pro Glu Lys Gln
    130                 135                 140

Ile Asp Glu His Leu Val Arg Ala Leu Tyr Arg Val Lys Lys Ile Arg
145                 150                 155                 160

Asn Ile Ile Glu Arg Glu Lys Asn Lys Gly Glu Gly Asp Lys Pro Thr
                165                 170                 175

Asn Pro Glu Asp Glu Glu Glu Leu Val Ile Glu Glu Glu Gln Glu Glu
            180                 185                 190

Glu Asp Gly Glu Gly Asp Glu Glu Asp Glu Ser Lys Val Glu Lys Ile
        195                 200                 205

Ile Thr Lys Tyr Gly Ile Met Lys Val Val Val Ser Thr Asn Asn Thr
    210                 215                 220

Ile Thr Lys Gly Cys Asp Phe Gly Asn Asn Val Val Asn Tyr Phe Ser
225                 230                 235                 240

Lys Pro Tyr Pro Val Glu Arg Tyr Gly Gly Ser Lys Val Cys Arg Ile
                245                 250                 255

Glu Ala Lys Pro Gly Glu Phe Val Gly Phe Lys Cys Ile Tyr Asp Asn
            260                 265                 270

Gln Gly Thr Val Glu Pro His Asn Cys Phe Asp Lys Val Phe Tyr Glu
        275                 280                 285

Gly Lys Glu Thr Asp Leu Gln Thr Leu Met Pro Gly Tyr Ile Ser Tyr
    290                 295                 300

Gly Asn Lys Gln Lys Gly Lys Tyr Ala Phe Tyr Leu Lys Leu Pro His
305                 310                 315                 320

Phe Val Gln His Ser Tyr Thr Val Gln Cys Lys Cys Met Ser Thr Val
                325                 330                 335

Ser Gln Phe Asp Asn Tyr Val Phe Glu Leu Ala Val Glu Gly Gly Glu
            340                 345                 350

Ser Asp Ile Val Ala Lys Ser Phe Gln Glu
        355                 360


<210> SEQ ID NO 18
<211> LENGTH: 1086
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 18

gaacacatct gcgattttac gaaggagaag taccttctgg ggaagaatga aaaggaatac     60

tgcgtggtga acgcgaagcc gtttgacagc gtaacattta tatgcccgaa gaaaatagga    120

gcacagtgct ttcagaatgt taacacgcta gacgatataa gtgcagacaa aatggaatcg    180

tccaagctgt ccatagatga gctgctatac gggtcgaccc tgtatggaga cacgctgctc    240

atatcgccca cggtgaagca gagcacaacc ttctactgtt tctgtaactt gcaaatggag    300

gacctgaaaa agtacctaaa gaagaggaga ctaaccaagg aaaaggaaaa tgcgaaaaag    360

aaatccactg tcaatgtgaa cgatttgaaa aatgcagacg aagatatgga ggtggtagtc    420

ccggagaagc aaatagatga acacctagtt agagcattat atagggtaaa aaaaattagg    480

aatataatag agcgtgaaaa gaacaaaggg gagggagata agcccacaaa tccggaagac    540

gaagaagaac tcgtaattga ggaggagcag gaagaagagg atggagaagg ggatgaagag    600
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gatgaaagta aagttgaaaa aatcattaca aagtatggaa taatgaaagt tgttgtttct    660

acgaataata caattactaa gggatgcgat ttcggaaata atgtggtgaa ttatttttct    720

aagccctacc ctgttgagag gtatggaggt agtaaagtct gcagaattga ggcgaagcca    780

ggagagtttg tcggcttcaa gtgcatatat gataaccagg gtaccgtcga accgcacaat    840

tgctttgata aggtctttta cgagggtaaa gaaaccgatt tgcagaccct catgcctggc    900

tatatatcat atggaaacaa gcagaagggg aaatacgcct tttacctgaa gctgccccac    960

tttgtgcaac acagctacac cgttcagtgc aagtgcatgt ccactgtgtc gcagttcgat   1020

aactacgtct tcgagttggc cgtggagggc ggcgagagcg atattgttgc caagtccttc   1080

caggag                                                              1086


<210> SEQ ID NO 19
<211> LENGTH: 427
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 19

Ile Ile Asn Ile Ile Leu Phe Tyr Phe Phe Leu Trp Val Lys Lys Ser
1               5                   10                  15

Ile Ser Asp Leu Leu Ser Ser Thr Gln Tyr Val Cys Asp Phe Tyr Phe
            20                  25                  30

Asn Pro Leu Thr Asn Val Lys Pro Thr Val Val Gly Ser Ser Glu Ile
        35                  40                  45

Tyr Glu Glu Val Gly Cys Thr Ile Asn Asn Pro Thr Leu Gly Asp His
    50                  55                  60

Ile Val Leu Ile Cys Pro Lys Lys Asn Asn Gly Asp Phe Ser Asn Ile
65                  70                  75                  80

Glu Ile Val Pro Thr Asn Cys Phe Glu Ser His Leu Tyr Ser Ala Tyr
                85                  90                  95

Lys Asn Asp Ser Ser Ala Tyr His Leu Glu Lys Leu Asp Ile Asp Lys
            100                 105                 110

Lys Tyr Ala Ile Asn Ser Ser Phe Ser Asp Phe Tyr Leu Lys Ile Leu
        115                 120                 125

Val Ile Pro Asn Glu Tyr Lys Ser His Lys Thr Ile Tyr Cys Arg Cys
    130                 135                 140

Asp Asn Ser Lys Thr Glu Lys Asn Ile Pro Gly Gln Asp Lys Ile Leu
145                 150                 155                 160

Lys Gly Lys Leu Gly Leu Val Lys Ile Ile Leu Arg Asn Gln Tyr Asn
                165                 170                 175

Asn Ile Ile Glu Leu Glu Lys Thr Lys His Ile Ile His Asn Lys Lys
            180                 185                 190

Asp Thr Tyr Lys Tyr Asp Ile Lys Leu Lys Glu Ser Asp Ile Leu Met
        195                 200                 205

Phe Tyr Met Lys Glu Glu Thr Ile Val Glu Ser Gly Asn Cys Glu Glu
    210                 215                 220

Ile Leu Asn Thr Lys Ile Asn Leu Leu Ser Asn Asn Asn Val Val Leu
225                 230                 235                 240

Lys Met Pro Ser Ile Phe Ile Asn Asn Ile Asn Cys Met Leu Ser Ser
                245                 250                 255

Gln Asp Gln Asn Asn Glu Lys Tyr Asn Ile Asn Leu Lys Ala Asp Lys
            260                 265                 270

Thr Lys His Ile Asp Gly Cys Asp Phe Thr Lys Pro Lys Gly Lys Gly
        275                 280                 285
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Ile Tyr Lys Asn Gly Phe Ile Ile Asn Asp Ile Pro Asn Glu Glu Glu
    290                 295                 300

Arg Ile Cys Thr Val His Leu Trp Asn Lys Lys Asn Gln Thr Ile Ala
305                 310                 315                 320

Gly Ile Lys Cys Pro Tyr Lys Leu Ile Pro Pro Tyr Cys Phe Lys His
                325                 330                 335

Val Leu Tyr Glu Lys Glu Ile Asp Ser Gln Lys Thr Tyr Lys Thr Phe
            340                 345                 350

Leu Leu Ser Asp Val Leu Asp Thr Pro Asn Ile Glu Tyr Tyr Gly Asn
        355                 360                 365

Asn Lys Glu Gly Met Tyr Met Leu Ala Leu Pro Thr Lys Pro Glu Lys
    370                 375                 380

Thr Asn Lys Ile Arg Cys Ile Cys Glu Gln Gly Gly Lys Lys Ala Val
385                 390                 395                 400

Met Glu Leu His Ile Ala Ser Thr Ser Thr Lys Tyr Ile Ser Met Phe
                405                 410                 415

Leu Ile Phe Phe Leu Ile Val Ile Phe Tyr Met
            420                 425


<210> SEQ ID NO 20
<211> LENGTH: 1282
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 20

cattataaat ataatattat tctatttctt cctttgggta aaaaaaagta ttagtgatct     60

attaagctca acacaatacg tatgtgattt ttattttaat cccctgacta atgttaagcc    120

aactgtagtt gggtcatctg aaatatacga agaagttgga tgtactataa acaaccctac    180

gttgggtgac catatagtat taatatgtcc taagaaaaat aatggagatt ttagtaatat    240

agaaatagta cctactaact gttttgaatc tcatttatat tctgcttata aaaatgattc    300

cagcgcatat catttagaaa aattagatat cgataaaaag tatgcaataa attcatcgtt    360

cagtgatttc tatttaaaaa ttttagttat acctaatgaa tataaaagtc ataaaactat    420

atattgtaga tgtgataata gtaaaacgga aaaaaatatc ccaggacaag ataaaatatt    480

aaaaggaaaa ttaggattag taaaaataat tttaagaaac caatataata atataataga    540

attagaaaaa acaaaacata ttatacataa taagaaggat acatataagt atgatataaa    600

attaaaagaa agtgatatac ttatgtttta tatgaaagaa gaaactattg tagaatctgg    660

aaattgtgaa gaaatattaa atactaaaat aaatctatta tcaaataata atgtggtttt    720

aaaaatgcct tccatattta taaataatat taattgtatg ctttcatctc aagatcaaaa    780

taatgaaaaa tataatataa atctaaaagc tgacaaaaca aaacatatag atgggtgtga    840

ttttacgaaa cctaaaggta aaggtatata caaaaatgga ttcataataa atgatatacc    900

aaatgaagaa gaacgtatat gtactgttca tctttggaat aaaaaaaatc aaactattgc    960

aggcattaaa tgtccatata aattaatacc accatattgt tttaaacatg tattatatga   1020

aaaagaaatc gattcgcaaa agacatataa aacatttcta ttaagtgatg tattagatac   1080

acctaatata gaatattatg gaaataataa ggaaggcatg tatatgttag ccttaccaac   1140

aaaaccagaa aaaacaaata aaattagatg tatttgtgaa caaggtggaa aaaaagcagt   1200

aatggaatta catatcgcat ctacatctac aaaatatatt agtatgtttc ttatattttt   1260

tctgattgta atttttttaca tg                                          1282
```

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<210> SEQ ID NO 21
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 21

Met Asn Lys Leu Tyr Ser Leu Phe Leu Phe Leu Phe Ile Gln Leu Ser
1 5 10 15

Ile Lys Tyr Asn Asn Ala Lys Val Thr Val Asp Thr Val Cys Lys Arg
20 25 30

Gly Phe Leu Ile Gln Met Ser Gly His Leu Glu Cys Lys Cys Glu Asn
35 40 45

Asp Leu Val Leu Val Asn Glu Glu Thr Cys Glu Glu Lys Val Leu Lys
50 55 60

Cys Asp Glu Lys Thr Val Asn Lys Pro Cys Gly Asp Phe Ser Lys Cys
65 70 75 80

Ile Lys Ile Asp Gly Asn Pro Val Ser Tyr Ala Cys Lys Cys Asn Leu
85 90 95

Gly Tyr Asp Met Val Asn Asn Val Cys Ile Pro Asn Glu Cys Lys Asn
100 105 110

Val Thr Cys Gly Asn Gly Lys Cys Ile Leu Asp Thr Ser Asn Pro Val
115 120 125

Lys Thr Ala Val Cys Ser Cys Asn Ile Gly Lys Val Pro Asn Val Gln
130 135 140

Asp Gln Asn Lys Cys Ser Lys Asp Gly Glu Thr Lys Cys Ser Leu Lys
145 150 155 160

Cys Leu Lys Glu Asn Glu Thr Cys Lys Ala Val Asp Gly Ile Tyr Lys
165 170 175

Cys Asp Cys Lys Asp Gly Phe Ile Ile Asp Asn Glu Ser Ser Ile Cys
180 185 190

Thr Ala Phe Ser Ala Tyr Asn Ile Leu Asn Leu Ser Ile Met Phe Ile
195 200 205

Leu Phe Ser Val Cys Phe Phe Ile Met
210 215

<210> SEQ ID NO 22
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 22

atgaataaac tttacagttt gtttcttttc cttttcattc aacttagcat aaaatataat 60

aatgcgaaag ttaccgtgga tactgtatgc aaaagaggat ttttaattca gatgagtggt 120

catttggaat gtaaatgtga aaatgatttg gtgttagtaa atgaagaaac atgtgaagaa 180

aaagttctga aatgtgacga aaagactgta aataaaccat gtggagattt ttccaaatgt 240

attaaaatag atggaaatcc cgtttcatac gcttgtaaat gtaatcttgg atatgatatg 300

gtaaataatg tttgtatacc aaatgaatgt aagaatgtaa cttgtggtaa cggtaaatgt 360

atattagata caagcaatcc tgttaaaact gcagtttgct catgtaatat aggcaaagtt 420

cccaatgtac aagatcaaaa taaatgttca aaagatggag aaaccaaatg ctcattaaaa 480

tgcttaaaag aaaatgaaac ctgtaaagct gttgatggaa tttataaatg tgattgtaaa 540

gatggattta taatagataa tgaaagctct atatgtactg ctttttcagc atataatatt 600

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ttaaatctaa gcattatgtt tatactattt tcagtatgct tttttataat gtaa 654

<210> SEQ ID NO 23
<211> LENGTH: 354
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 23

Met Lys Ser Phe Ile Asn Ile Thr Leu Ser Leu Phe Leu Leu His Leu
1 5 10 15

Tyr Ile Tyr Ile Asn Asn Val Ala Ser Lys Glu Ile Val Lys Lys Tyr
20 25 30

Asn Leu Asn Leu Arg Asn Ala Ile Leu Asn Asn Asn Ser Gln Ile Glu
35 40 45

Asn Glu Glu Asn Val Asn Thr Thr Ile Thr Gly Asn Asp Phe Ser Gly
50 55 60

Gly Glu Phe Leu Trp Pro Gly Tyr Thr Glu Glu Leu Lys Ala Lys Lys
65 70 75 80

Ala Ser Glu Asp Ala Glu Lys Ala Ala Asn Asp Ala Glu Asn Ala Ser
85 90 95

Lys Glu Ala Glu Glu Ala Ala Lys Glu Ala Val Asn Leu Lys Glu Ser
100 105 110

Asp Lys Ser Tyr Thr Lys Ala Lys Glu Ala Cys Thr Ala Ala Ser Lys
115 120 125

Ala Lys Lys Ala Val Glu Thr Ala Leu Lys Ala Lys Asp Asp Ala Glu
130 135 140

Lys Ser Ser Lys Ala Asp Ser Ile Ser Thr Lys Thr Lys Glu Tyr Ala
145 150 155 160

Glu Lys Ala Lys Asn Ala Tyr Glu Lys Ala Lys Asn Ala Tyr Gln Lys
165 170 175

Ala Asn Gln Ala Val Leu Lys Ala Lys Glu Ala Ser Ser Tyr Asp Tyr
180 185 190

Ile Leu Gly Trp Glu Phe Gly Gly Gly Val Pro Glu His Lys Lys Glu
195 200 205

Glu Asn Met Leu Ser His Leu Tyr Val Ser Ser Lys Asp Lys Glu Asn
210 215 220

Ile Ser Lys Glu Asn Asp Asp Val Leu Asp Glu Lys Glu Glu Glu Ala
225 230 235 240

Glu Glu Thr Glu Glu Glu Glu Leu Glu Glu Lys Asn Glu Glu Glu Thr
245 250 255

Glu Ser Glu Ile Ser Glu Asp Glu Glu Glu Glu Glu Glu Glu Glu Glu
260 265 270

Lys Glu Glu Glu Asn Asp Lys Lys Lys Glu Gln Glu Lys Glu Gln Ser
275 280 285

Asn Glu Asn Asn Asp Gln Lys Lys Asp Met Glu Ala Gln Asn Leu Ile
290 295 300

Ser Lys Asn Gln Asn Asn Asn Glu Lys Asn Val Lys Glu Ala Ala Glu
305 310 315 320

Ser Ile Met Lys Thr Leu Ala Gly Leu Ile Lys Gly Asn Asn Gln Ile
325 330 335

Asp Ser Thr Leu Lys Asp Leu Val Glu Glu Leu Ser Lys Tyr Phe Lys
340 345 350

Asn His

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<210> SEQ ID NO 24
<211> LENGTH: 1065
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 24

atgaaaagtt ttataaatat tactctttca ttatttttgt tacatttata tatttatata 60

aataatgttg ctagtaaaga aattgtaaaa aaatataatc ttaacttaag aaatgcaata 120

ttgaataata attctcaaat agaaaatgaa gaaaatgtaa atactacaat tactggtaat 180

gattttagtg gtggagaatt tttgtggcct ggttatacgg aagaattaaa agctaaaaaa 240

gcttccgaag atgctgaaaa agctgctaat gatgctgaaa atgcttcaaa agaggcagaa 300

gaagctgcta aagaagcagt aaatttaaag gaatctgata aatcttatac aaaagcaaaa 360

gaagcatgta cagctgcttc aaaggcaaag aaagctgttg aaactgcttt aaaggcaaaa 420

gatgatgctg aaaaatcttc aaaagctgat agtatttcta caaaaacaaa agaatatgct 480

gaaaaagcaa aaaatgctta tgaaaaggca aaaaatgctt atcaaaaagc aaaccaagct 540

gttttaaaag caaaagaagc ttctagttat gattatattt taggttggga atttggagga 600

ggcgttccag aacacaaaaa agaagaaaat atgttatcac atttatatgt ttcttcaaag 660

gataaggaaa atatatctaa ggaaaatgat gatgtattag atgagaagga agaagaggca 720

gaagaaacag aagaagaaga acttgaagaa aaaaatgaag aagaaacaga atcagaaata 780

agtgaagatg aagaagaaga agaagaagaa gaagaaaagg aagaagaaaa tgacaaaaaa 840

aaagaacaag aaaaagaaca aagtaatgaa aataatgatc aaaaaaaaga tatggaagca 900

cagaatttaa tttctaaaaa ccagaataat aatgagaaaa acgtaaaaga agctgctgaa 960

agcatcatga aaactttagc tggtttaatc aagggaaata atcaaataga ttctaccttа 1020

aaagatttag tagaagaatt atccaaatat tttaaaaatc attaa 1065

<210> SEQ ID NO 25
<211> LENGTH: 630
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 25

Ala Glu Arg Ser Thr Ser Glu Asn Arg Asn Lys Arg Ile Gly Gly Pro
1 5 10 15

Lys Leu Arg Gly Asn Val Thr Ser Asn Ile Lys Phe Pro Ser Asp Asn
20 25 30

Lys Gly Lys Ile Ile Arg Gly Ser Asn Asp Lys Leu Asn Lys Asn Ser
35 40 45

Glu Asp Val Leu Glu Gln Ser Glu Lys Ser Leu Val Ser Glu Asn Val
50 55 60

Pro Ser Gly Leu Asp Ile Asp Asp Ile Pro Lys Glu Ser Ile Phe Ile
65 70 75 80

Gln Glu Asp Gln Glu Gly Gln Thr His Ser Glu Leu Asn Pro Glu Thr
85 90 95

Ser Glu His Ser Lys Asp Leu Asn Asn Asn Gly Ser Lys Asn Glu Ser
100 105 110

Ser Asp Ile Ile Ser Glu Asn Asn Lys Ser Asn Lys Val Gln Asn His
115 120 125

Phe Glu Ser Leu Ser Asp Leu Glu Leu Leu Glu Asn Ser Ser Gln Asp
130 135 140

Asn Leu Asp Lys Asp Thr Ile Ser Thr Glu Pro Phe Pro Asn Gln Lys

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145                 150                 155                 160

His Lys Asp Leu Gln Gln Asp Leu Asn Asp Glu Pro Leu Glu Pro Phe
                165                 170                 175

Pro Thr Gln Ile His Lys Asp Tyr Lys Glu Lys Asn Leu Ile Asn Glu
            180                 185                 190

Glu Asp Ser Glu Pro Phe Pro Arg Gln Lys His Lys Lys Val Asp Asn
        195                 200                 205

His Asn Glu Glu Lys Asn Val Phe His Glu Asn Gly Ser Ala Asn Gly
    210                 215                 220

Asn Gln Gly Ser Leu Lys Leu Lys Ser Phe Asp Glu His Leu Lys Asp
225                 230                 235                 240

Glu Lys Ile Glu Asn Glu Pro Leu Val His Glu Asn Leu Ser Ile Pro
                245                 250                 255

Asn Asp Pro Ile Glu Gln Ile Leu Asn Gln Pro Glu Gln Glu Thr Asn
            260                 265                 270

Ile Gln Glu Gln Leu Tyr Asn Glu Lys Gln Asn Val Glu Glu Lys Gln
        275                 280                 285

Asn Ser Gln Ile Pro Ser Leu Asp Leu Lys Glu Pro Thr Asn Glu Asp
    290                 295                 300

Ile Leu Pro Asn His Asn Pro Leu Glu Asn Ile Lys Gln Ser Glu Ser
305                 310                 315                 320

Glu Ile Asn His Val Gln Asp His Ala Leu Pro Lys Glu Asn Ile Ile
                325                 330                 335

Asp Lys Leu Asp Asn Gln Lys Glu His Ile Asp Gln Ser Gln His Asn
            340                 345                 350

Ile Asn Val Leu Gln Glu Asn Asn Ile Asn Asn His Gln Leu Glu Pro
        355                 360                 365

Gln Glu Lys Pro Asn Ile Glu Ser Phe Glu Pro Lys Asn Ile Asp Ser
    370                 375                 380

Glu Ile Ile Leu Pro Glu Asn Val Glu Thr Glu Glu Ile Ile Asp Asp
385                 390                 395                 400

Val Pro Ser Pro Lys His Ser Asn His Glu Thr Phe Glu Glu Glu Thr
                405                 410                 415

Ser Glu Ser Glu His Glu Glu Ala Val Ser Glu Lys Asn Ala His Glu
            420                 425                 430

Thr Val Glu His Glu Glu Thr Val Ser Gln Glu Ser Asn Pro Glu Lys
        435                 440                 445

Ala Asp Asn Asp Gly Asn Val Ser Gln Asn Ser Asn Asn Glu Leu Asn
    450                 455                 460

Glu Asn Glu Phe Val Glu Ser Glu Lys Ser Glu His Glu Ala Arg Ser
465                 470                 475                 480

Lys Pro Lys Tyr Glu Lys Lys Val Ile His Gly Cys Asn Phe Ser Ser
                485                 490                 495

Asn Val Ser Ser Lys His Thr Phe Thr Asp Ser Leu Asp Ile Ser Leu
            500                 505                 510

Val Asp Asp Ser Ala His Ile Ser Cys Asn Val His Leu Ser Glu Pro
        515                 520                 525

Lys Tyr Asn His Leu Val Gly Leu Asn Cys Pro Gly Asp Ile Ile Pro
    530                 535                 540

Asp Cys Phe Phe Gln Val Tyr Gln Pro Glu Ser Glu Glu Leu Glu Pro
545                 550                 555                 560

Ser Asn Ile Val Tyr Leu Asp Ser Gln Ile Asn Ile Gly Asp Ile Glu
                565                 570                 575
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Tyr Tyr Glu Asp Ala Glu Gly Asp Asp Lys Ile Lys Leu Phe Gly Ile
            580                 585                 590

Val Gly Ser Ile Pro Lys Thr Thr Ser Phe Thr Cys Ile Cys Lys Lys
        595                 600                 605

Asp Lys Lys Ser Ala Tyr Met Thr Val Thr Ile Asp Ser Ala Arg Ser
    610                 615                 620

His His His His His His
625                 630
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<210> SEQ ID NO 26
<211> LENGTH: 1977
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 26

```
atgaaattta ataaaaaaag agttgcaata gccacgttta ttgctttgat atttgtaagt     60

ttttttacaa tatcatcaat ccaagatgct caagcagccg aaagatccac aagtgagaat    120

agaaataaac gaatcggggg tcctaaatta aggggtaatg ttacaagtaa tataaagttc    180

ccatcagata acaaaggtaa aattataaga ggttcgaatg ataaacttaa taaaaactct    240

gaagatgttt tagaacaaag cgaaaaatcg cttgtttcag aaaatgttcc tagtggatta    300

gatatagatg atatccctaa agaatctatt tttattcaag aagatcaaga aggtcaaact    360

cattctgaat taaatcctga aacatcagaa catagtaaag atttaaataa taatggttca    420

aaaaatgaat ctagtgatat tatttcagaa aataataaat caaataaagt acaaaatcat    480

tttgaatcat tatcagattt agaattactt gaaaattcct cacaagataa tttagacaaa    540

gatacaattt caacagaacc ttttcctaat caaaaacata aagacttaca acaagattta    600

aatgatgaac ctttagaacc ctttcctaca caaatacata aagattataa agaaaaaaat    660

ttaataaatg aagaagattc agaaccattt cccagacaaa agcataaaaa ggtagacaat    720

cataatgaag aaaaaaacgt atttcatgaa aatggttctg caaatggtaa tcaaggaagt    780

ttgaaactta aatcattcga tgaacattta aaagatgaaa aaatagaaaa tgaaccactt    840

gttcatgaaa atttatccat accaaatgat ccaatagaac aaatattaaa tcaacctgaa    900

caagaaacaa atatccagga acaattgtat aatgaaaaac aaaatgttga agaaaaacaa    960

aattctcaaa taccttcgtt agatttaaaa gaaccaacaa atgaagatat tttaccaaat   1020

cataatccat tagaaaatat aaaacaaagt gaatcagaaa taaatcatgt acaagatcat   1080

gcgctaccaa aagagaatat aatagacaaa cttgataatc aaaaagaaca catcgatcaa   1140

tcacaacata atataaatgt attacaagaa aataacataa acaatcacca attagaacct   1200

caagagaaac ctaatattga atcgtttgaa cctaaaaata tagattcaga aattattctt   1260

cctgaaaatg ttgaaacaga agaaataata gatgatgtgc cttcccctaa acattctaac   1320

catgaaacat ttgaagaaga aacaagtgaa tctgaacatg aagaagccgt atctgaaaaa   1380

aatgcccacg aaactgtcga acatgaagaa actgtgtctc aagaaagcaa tcctgaaaaa   1440

gctgataatg atggaaatgt atctcaaaac agcaacaacg aattaaatga aaatgaattc   1500

gttgaatcgg aaaaaagcga gcatgaagca agatccgaaa aaaaagtcat acacggatgt   1560

aacttctctt caaatgttag ttctaaacat acttttacag atagtttaga tatttcttta   1620

gttgatgata gtgcacatat ttcatgtaac gtacatttgt ctgaaccaaa atataatcat   1680

ttggtaggtt taaattgtcc tggtgatatt ataccagatt gctttttttca agtatatcaa   1740
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cctgaatcag aagaacttga accatccaac attgtttatt tagattcaca aataaatata   1800

ggagatattg aatattatga agatgctgaa ggagatgata aaattaaatt atttggtata   1860

gttggaagta taccaaaaac gacatctttt acttgtatat gtaagaagga taaaaaaagt   1920

gcttatatga cagttactat agattcagca agatctcatc accatcatca ccattag      1977


<210> SEQ ID NO 27
<211> LENGTH: 727
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 27

Ala Glu Arg Ser Thr Ser Glu Asn Arg Asn Lys Arg Ile Gly Gly Pro
1               5                   10                  15

Lys Leu Arg Gly Asn Val Thr Ser Asn Ile Lys Phe Pro Ser Asp Asn
            20                  25                  30

Lys Gly Lys Ile Ile Arg Gly Ser Asn Asp Lys Leu Asn Lys Asn Ser
        35                  40                  45

Glu Asp Val Leu Glu Gln Ser Glu Lys Ser Leu Val Ser Glu Asn Val
    50                  55                  60

Pro Ser Gly Leu Asp Ile Asp Asp Ile Pro Lys Glu Ser Ile Phe Ile
65                  70                  75                  80

Gln Glu Asp Gln Glu Gly Gln Thr His Ser Glu Leu Asn Pro Glu Thr
                85                  90                  95

Ser Glu His Ser Lys Asp Leu Asn Asn Asn Gly Ser Lys Asn Glu Ser
            100                 105                 110

Ser Asp Ile Ile Ser Glu Asn Asn Lys Ser Asn Lys Val Gln Asn His
        115                 120                 125

Phe Glu Ser Leu Ser Asp Leu Glu Leu Leu Glu Asn Ser Ser Gln Asp
    130                 135                 140

Asn Leu Asp Lys Asp Thr Ile Ser Thr Glu Pro Phe Pro Asn Gln Lys
145                 150                 155                 160

His Lys Asp Leu Gln Gln Asp Leu Asn Asp Glu Pro Leu Glu Pro Phe
                165                 170                 175

Pro Thr Gln Ile His Lys Asp Tyr Lys Glu Lys Asn Leu Ile Asn Glu
            180                 185                 190

Glu Asp Ser Glu Pro Phe Pro Arg Gln Lys His Lys Lys Val Asp Asn
        195                 200                 205

His Asn Glu Glu Lys Asn Val Phe His Glu Asn Gly Ser Ala Asn Gly
    210                 215                 220

Asn Gln Gly Ser Leu Lys Leu Lys Ser Phe Asp Glu His Leu Lys Asp
225                 230                 235                 240

Glu Lys Ile Glu Asn Glu Pro Leu Val His Glu Asn Leu Ser Ile Pro
                245                 250                 255

Asn Asp Pro Ile Glu Gln Ile Leu Asn Gln Pro Glu Gln Glu Thr Asn
            260                 265                 270

Ile Gln Glu Gln Leu Tyr Asn Glu Lys Gln Asn Val Glu Glu Lys Gln
        275                 280                 285

Asn Ser Gln Ile Pro Ser Leu Asp Leu Lys Glu Pro Thr Asn Glu Asp
    290                 295                 300

Ile Leu Pro Asn His Asn Pro Leu Glu Asn Ile Lys Gln Ser Glu Ser
305                 310                 315                 320

Glu Ile Asn His Val Gln Asp His Ala Leu Pro Lys Glu Asn Ile Ile
                325                 330                 335
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Asp Lys Leu Asp Asn Gln Lys Glu His Ile Asp Gln Ser Gln His Asn
            340                 345                 350

Ile Asn Val Leu Gln Glu Asn Asn Ile Asn Asn His Gln Leu Glu Pro
        355                 360                 365

Gln Glu Lys Pro Asn Ile Glu Ser Phe Glu Pro Lys Asn Ile Asp Ser
    370                 375                 380

Glu Ile Ile Leu Pro Glu Asn Val Glu Thr Glu Glu Ile Ile Asp Asp
385                 390                 395                 400

Val Pro Ser Pro Lys His Ser Asn His Glu Thr Phe Glu Glu Glu Thr
                405                 410                 415

Ser Glu Ser Glu His Glu Glu Ala Val Ser Glu Lys Asn Ala His Glu
            420                 425                 430

Thr Val Glu His Glu Glu Thr Val Ser Gln Glu Ser Asn Pro Glu Lys
        435                 440                 445

Ala Asp Asn Asp Gly Asn Val Ser Gln Asn Ser Asn Asn Glu Leu Asn
    450                 455                 460

Glu Asn Glu Phe Val Glu Ser Glu Lys Ser Glu His Glu Ala Arg Ser
465                 470                 475                 480

Lys Thr Lys Glu Tyr Ala Glu Lys Ala Lys Asn Ala Tyr Glu Lys Ala
                485                 490                 495

Lys Asn Ala Tyr Gln Lys Ala Asn Gln Ala Val Leu Lys Ala Lys Glu
            500                 505                 510

Ala Ser Ser Tyr Asp Tyr Ile Leu Gly Trp Glu Phe Gly Gly Gly Val
        515                 520                 525

Pro Glu His Lys Lys Glu Glu Asn Met Leu Ser His Leu Tyr Val Ser
    530                 535                 540

Ser Lys Asp Lys Glu Asn Ile Ser Lys Glu Asn Asp Asp Val Leu Asp
545                 550                 555                 560

Glu Lys Glu Glu Glu Ala Glu Glu Thr Glu Glu Glu Glu Leu Glu Arg
                565                 570                 575

Ser Lys Pro Lys Tyr Glu Lys Lys Val Ile His Gly Cys Asn Phe Ser
            580                 585                 590

Ser Asn Val Ser Ser Lys His Thr Phe Thr Asp Ser Leu Asp Ile Ser
        595                 600                 605

Leu Val Asp Asp Ser Ala His Ile Ser Cys Asn Val His Leu Ser Glu
    610                 615                 620

Pro Lys Tyr Asn His Leu Val Gly Leu Asn Cys Pro Gly Asp Ile Ile
625                 630                 635                 640

Pro Asp Cys Phe Phe Gln Val Tyr Gln Pro Glu Ser Glu Glu Leu Glu
                645                 650                 655

Pro Ser Asn Ile Val Tyr Leu Asp Ser Gln Ile Asn Ile Gly Asp Ile
            660                 665                 670

Glu Tyr Tyr Glu Asp Ala Glu Gly Asp Asp Lys Ile Lys Leu Phe Gly
        675                 680                 685

Ile Val Gly Ser Ile Pro Lys Thr Thr Ser Phe Thr Cys Ile Cys Lys
    690                 695                 700

Lys Asp Lys Lys Ser Ala Tyr Met Thr Val Thr Ile Asp Ser Ala Arg
705                 710                 715                 720

Ser His His His His His His
                725
```

<210> SEQ ID NO 28
<211> LENGTH: 2268
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 28

atgaaattta ataaaaaaag agttgcaata gccacgttta ttgctttgat atttgtaagt 60

ttttttacaa tatcatcaat ccaagatgct caagcagccg aaagatccac aagtgagaat 120

agaaataaac gaatcggggg tcctaaatta aggggtaatg ttacaagtaa tataaagttc 180

ccatcagata acaaaggtaa aattataaga ggttcgaatg ataaacttaa taaaaactct 240

gaagatgttt tagaacaaag cgaaaaatcg cttgtttcag aaaatgttcc tagtggatta 300

gatatagatg atatccctaa agaatctatt tttattcaag aagatcaaga aggtcaaact 360

cattctgaat taaatcctga aacatcagaa catagtaaag atttaaataa taatggttca 420

aaaaatgaat ctagtgatat tatttcagaa aataataaat caaataaagt acaaaatcat 480

tttgaatcat tatcagattt agaattactt gaaaattcct cacaagataa tttagacaaa 540

gatacaattt caacagaacc ttttcctaat caaaaacata aagacttaca acaagattta 600

aatgatgaac ctttagaacc ctttcctaca caaatacata aagattataa agaaaaaaat 660

ttaataaatg aagaagattc agaaccattt cccagacaaa agcataaaaa ggtagacaat 720

cataatgaag aaaaaaacgt atttcatgaa aatggttctg caaatggtaa tcaaggaagt 780

ttgaaactta aatcattcga tgaacattta aaagatgaaa aaatagaaaa tgaaccactt 840

gttcatgaaa atttatccat accaaatgat ccaatagaac aaatattaaa tcaacctgaa 900

caagaaacaa atatccagga acaattgtat aatgaaaaac aaaatgttga agaaaaacaa 960

aattctcaaa taccttcgtt agatttaaaa gaaccaacaa atgaagatat tttaccaaat 1020

cataatccat tagaaaatat aaaacaaagt gaatcagaaa taaatcatgt acaagatcat 1080

gcgctaccaa aagagaatat aatagacaaa cttgataatc aaaaagaaca catcgatcaa 1140

tcacaacata atataaatgt attacaagaa aataacataa acaatcacca attagaacct 1200

caagagaaac ctaatattga atcgtttgaa cctaaaaata tagattcaga aattattctt 1260

cctgaaaatg ttgaaacaga agaaataata gatgatgtgc cttcccctaa acattctaac 1320

catgaaacat ttgaagaaga aacaagtgaa tctgaacatg aagaagccgt atctgaaaaa 1380

aatgcccacg aaactgtcga acatgaagaa actgtgtctc aagaaagcaa tcctgaaaaa 1440

gctgataatg atggaaatgt atctcaaaac agcaacaacg aattaaatga aaatgaattc 1500

gttgaatcgg aaaaaagcga gcatgaagca agatccaaaa caaaagaata tgctgaaaaa 1560

gcaaaaaatg cttatgaaaa ggcaaaaaat gcttatcaaa aagcaaacca agctgtttta 1620

aaagcaaaag aagcttctag ttatgattat attttaggtt gggaatttgg aggaggcgtt 1680

ccagaacaca aaaaagaaga aaatatgtta tcacatttat atgtttcttc aaaggataag 1740

gaaaatatat ctaaggaaaa tgatgatgta ttagatgaga aggaagaaga ggcagaagaa 1800

acagaagaag aagaacttga aagatccgaa aaaaaagtca tacacggatg taacttctct 1860

tcaaatgtta gttctaaaca tacttttaca gatagtttag atatttcttt agttgatgat 1920

agtgcacata tttcatgtaa cgtacatttg tctgaaccaa aatataatca tttggtaggt 1980

ttaaattgtc ctggtgatat tataccagat tgctttttttc aagtatatca acctgaatca 2040

gaagaacttg aaccatccaa cattgtttat ttagattcac aaataaatat aggagatatt 2100

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gaatattatg aagatgctga aggagatgat aaaattaaat tatttggtat agttggaagt   2160

ataccaaaaa cgacatcttt tacttgtata tgtaagaagg ataaaaaaag tgcttatatg   2220

acagttacta tagattcagc aagatctcat caccatcatc accattag                2268
```

The invention claimed is:

1. A method of producing a cysteine-rich protein, comprising expressing a cysteine-rich protein fused to a glutamate-rich protein in a lactic acid bacterial system, where the formation of monomeric fusion protein is enhanced by controlling the redox potential in the lactic acid bacterial production medium by adding the reduced form of a sulfhydryl containing compound to a concentration of 5-20 mM.

2. The method according to claim **1**, where the glutamate-rich protein is GLURP or part of GLURP.

3. The method according to claim **1** where the lactic acid bacterium is *Lactococcus lactis*.

4. The method according to claim **1** where said sulfhydryl containing compound is L-cysteine.

5. The method according to claim **1** where the cysteine-rich protein originates from *Plasmodium falciparum*.

6. The method according to claim **5** where the cysteine-rich protein is Pfs48/45, Pfs25, Pfs230, Pfs47, EBA175, a member of the PfEMP1, RIFIN or STEVOR protein families or a fragment or a homologue hereof.

7. The method according to claim **1** where the correct folding of the cysteine rich protein is enhanced by addition of reduced and oxidized forms of a sulfhydryl containing compound capable of reducing or oxidixing cystines or cysteines in proteins to the buffer during the down-stream processing.

8. The method according to claim **7** where 1-10 mM of the reduced form and 0.1-5 mM of the oxidized form of the sulfhydryl containing compound is added.

9. The method according to claim **4** wherein L-cysteine is added to the medium to a concentration of about 10 mM.

10. The method according to claim **7**, wherein said sulfhydryl containing compound is L-cysteine, DTT, glutathione, TCEP, or cysteamine.

11. The method according to claim **7**, wherein said sulfhydryl containing compound is L-cysteine.

12. A method of producing a cysteine-rich protein, comprising expressing a cysteine-rich protein fused to a glutamate-rich protein in a lactic acid bacterial system, where the formation of monomeric fusion protein is enhanced by controlling the redox potential in the lactic acid bacterial production medium by adding the reduced form of L-cysteine, DTT, glutathione, TCEP, or cysteamine to a concentration of 5-20 mM.

13. The method according to claim **12**, wherein said reduced form of L-cysteine, DTT, glutathione, TCEP, or cysteamine is added to the medium to a concentration of about 10 mM.

14. The method according to claim **13**, wherein L-cysteine is added to the medium to a concentration of about 10 mM.

15. The method according to claim **12**, where the glutamate-rich protein is GLURP or part of GLURP.

16. The method according to claim **12**, where the lactic acid bacterium is *Lactococcus lactis*.

17. The method according to claim **12**, where the cysteine-rich protein originates from *Plasmodium falciparum*.

18. The method according to claim **17**, where the cysteine-rich protein is Pfs48/45, Pfs25, Pfs230, Pfs47, EBA175, a member of the PfEMP1, RIFIN or STEVOR protein families or a fragment or a homologue hereof.

19. The method according to claim **12**, where the correct folding of the cysteine rich protein is enhanced by addition of reduced and oxidized forms of a small sulfhydryl containing compound capable of reducing or oxidixing cystines or cysteines in proteins to the buffer during the down-stream processing.

20. The method according to claim **19**, where 1-10 mM of the reduced form and 0.1-5 mM of the oxidized form of the sulfhydryl containing compound is added.

* * * * *